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Treatment of *Helicobacter pylori* Infection 2011

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Abstract

This article reviews the literature published pertaining to *Helicobacter pylori* eradication over the last year. The general perception among clinicians and academics engaged in research on *H. pylori* has been that eradication rates for first-line therapies are falling, although some data published this year have cast doubt on this. The studies published this year have therefore focussed on developing alternative strategies for the first-line eradication of *H. pylori*. In this regard, clear evidence now exists that both levofloxacin and bismuth are viable options for first-line therapy. The sequential and ''concomitant'' regimes have also been studied in new settings and may have a role in future algorithms also. In addition, data have emerged that the probiotic *Saccharomyces boulardii* may be a useful adjunct to antibiotic therapy. Other studies promote individualized therapies based on host polymorphisms, age, and other such demographic factors.

Over the last decade, it has been widely reported that the success of *Helicobacter pylori* eradication treatment is falling. A steady decline was observed in the number of patients achieving eradication with standard first-line triple therapy of two antibiotics and a proton pump inhibitor [1–3]. It now appears that the first-line eradication therapies most commonly used in everyday clinical practice fall considerably short of the 80% intention-to-treat (ITT) eradication rates that are considered the minimal acceptable levels as recommended in the Maastricht guidelines [4]. Interestingly, two studies emerged from Asian centers in the last 12 months, which show that, in this part of the world at least, eradication levels using standard therapies remain close to 80%. A Malaysian study showed a standard 1-week pantoprazole, amoxycillin, and clarithromycin regimen to be well tolerated and highly efficacious with a per-protocol eradication rate of 84% [5]. A Japanese study showed remarkably consistent per-protocol eradication rates from 2001 to 2009 fluctuating between 75 and 78% for standard 7-day triple-therapy regimens [6]. A limit of many studies especially those including clarithromycin or levofloxacin is that *H. pylori* susceptibility to the drugs, which is the main prediction of failure, was not tested.

Levofloxacin

The use of levofloxacin as a first-line therapy has been examined in great depth in the last year. Levofloxacin may be used as a substitute for clarithromycin in either a standard triple or sequential regimen. A large study comparing the antibiotics in either regimen shows a clear advantage to levofloxacin in both combinations. Per-protocol cure rates for triple therapy were 66% for omeprazole–clarithromycin–amoxycillin compared with 83% for omeprazole–levofloxacin–amoxycillin and 81% for omeprazole–amoxycillin–clarithromycin–metronidazole vs 85% for omeprazole–amoxycillin–levofloxacin–metronidazole, with no difference in compliance rates or adverse events [7]. It has been proposed that sequential levofloxacin-based regimens are of most benefit in areas where clarithromycin resistance is in excess of 15%, and another study in such an area showed eradication rates of 81% with clarithromycin sequential therapy compared with 96% with levofloxacin sequential therapy. A third arm in this study looked at the dose of levofloxacin required and illustrated no benefit in increasing the dose from 250 to 500 mg [8]. Indeed, another study went so far as to suggest that once-daily dosing of a levofloxacin-based triple regimen may be as efficacious as twice daily [9]. The literature from Asia also seems to support levofloxacin as a good alternative first-line therapy. A study on a triple regimen showed per-protocol eradication rates of 78% for standard clarithromycin-containing therapies compared with 83% for a levofloxacin-based regimen [10]. Another study from the Middle East looked at whether combining clarithromycin and levofloxacin in the same regimen could be

effective and found a 90% eradication rate for a combined clarithromycin–levofloxacin–esomeprazole regimen compared with 85% for levofloxacin–amoxycillin–esomeprazole and 79% for clarithromycin–amoxycillin–esomeprazole with no difference in the incidence or severity of adverse events [11]. The question remains, though, as to whether levofloxacin's best place is as first- or second-line therapy. A crossover study published last year indicates that a clarithromycin–amoxycillin–lansoprazole regimen performs better than a levofloxacin–amoxycillin–lansoprazole regimen as first-line therapy (84 vs 74%), but this is reversed in second-line therapy (77 vs 60%) [12]. The eradication rate was significantly lower in the presence of levofloxacin resistance in the levofloxacin–amoxycillin–lansoprazole group (50 vs 84%). Resistance to levofloxacin is a growing problem with a report of unpublished data suggesting that levofloxacin resistance in Spain may have increased from 6% to more than 25% over the last 5 years [13]. Another role of levofloxacin may be in the treatment of patients with penicillin allergies. In a study of a levofloxacin-based regimen used in penicillin-allergic patients after omeprazole–clarithromycin–metronidazole had been unsuccessful, eradication rates of 73% were noted [14]. Few data are available on the role of other fluoroquinolones in the management of *H. pylori* infection. However, a meta-analysis of moxifloxacin-based second-line regimens showed it to be both better tolerated and more efficacious (75 vs 61%) than a bismuth-containing quadruple therapy [15].

Bismuth

The role of bismuth as both a first- and second-line eradication agent has also been examined this year. A meta-analysis on the topic illustrated that bismuth-based quadruple therapy and standard triple therapy had similar rates of eradication and side effect profiles [16]. Quadruple therapy is associated with high cure rates, yet its complex administration protocol hampers its acceptability for general use. A recent study has assessed the efficacy and safety of a novel, single-capsule bismuth-containing quadruple therapy. This multicenter study of a 10-day bismuth-based quadruple therapy (bismuth–metronidazole–tetracycline–omeprazole) as first-line therapy showed an eradication rate of 80% in the quadruple therapy group versus 55% for the standard 7-day triple-therapy group [17]. However, recent commentaries have suggested that the methodology used in this study was quite conservative. Indeed, those having follow-up urea breath testing outside of the time frame were considered as having persistent infection and if these cases were not included the rate of cure went up to 93% via intention-to-treat analysis [18]. Indeed, the question remains whether this new mode of administration could not lead to better results than drugs prescribed individually. Longer durations of bismuth-based therapy appear to be more efficacious. A study of a bismuth–omeprazole–amoxycillin and clarithromycin regimen showed superior eradication of 94% in a group treated for 14 days compared with 80% for a group treated for 7 days [19]. Bismuth also appears to be a viable option when standard first-line triple therapy has failed. In one study of patients unsuccessfully treated with triple therapy, eradication rates of 77% were obtained for 1 week of bismuth-based quadruple therapy and 94% for 2 weeks (per-protocol) [20]. This study showed, though, that adverse events were more than twice as common in the 14-day group, although no decrease in compliance was seen.

Sequential Therapy

The primary goal of the sequential regimen is to overcome clarithromycin resistance. During the first 5 days of therapy, amoxycillin is taken with proton pump inhibitors (PPI) with the intention to weaken the bacterial cell wall, which prevents the formation of the channels that block clarithromycin from binding to the bacterium and hence cause resistance to the antibiotic. Then, in the second phase of therapy, amoxycillin is discontinued and clarithromycin and a nitroimidazole are added for a further 5 days. Proton pump inhibitor is continued throughout treatment. Although this regimen was largely heralded as being able to overcome clarithromycin resistance, recent studies have shown in fact that it can be influenced by clarithromycin resistance and that when the clarithromycin resistance mutation exists, eradication rates are lower (65% vs 98%) [21]. Evidence for the efficacy of sequential therapy had previously been heavily weighted toward studies carried out on Italian patients [22]. The last year has seen a greater number of studies carried out in other parts of the world. One study from Thailand reported a 95% eradication rate for 10-day sequential therapy [23]. Another study from Turkey where eradication rates are low showed 78% eradication for sequential therapy versus 53% for standard triple therapy based on a per-protocol analysis [24]. In China, a comparative study showed eradication rates of 83% for bismuth-based quadruple therapy and 81% for standard triple therapy with the most impressive eradication rate of 89% for sequential therapy [25]. Further study showed that continuing amoxycillin for the entire duration of the sequential therapy did not increase the eradication rate [26]. Furthermore, extending the duration of

sequential therapy from 10 to 14 days was not associated with an increased eradication rate [27]. ''Concomitant'' or quadruple therapy has also been proposed. It is intended to reduce the complexity associated with sequential therapy by having the patient take all three antibiotics for the entire 10-day duration of therapy. When compared with standard triple therapy in a meta-analysis, ''concomitant'' therapy had an ITT eradication rate of 90%, superior to standard triple therapy with a pooled odds ratio of 2.86 [28]. It must be emphasized that most of the studies included in this meta-analysis were indeed performed at a time when clarithromycin resistance was not as high as it is now. When compared with the sequential regimen, ''concomitant'' administration of the same drugs provides similar results in terms of efficacy and safety. The sequential administration protocol may produce unnecessary complexity for both patients and physicians compared with concurrent prescription of all the medications from the outset [29].

Furazolidone

Furazolidone has been proposed as an alternative to clarithromycin as it is economic in terms of cost and resistance but its use remains uncommon. An Iranian study showed that furazolidone performed as well with clarithromycin as it did with metronidazole in a bismuth-containing regimen although neither was superior to standard triple therapy in this cohort [30].

The Role of Probiotics and other Adjuncts to Therapy

Probiotics have been proposed as a useful adjunct for *H. pylori* eradication therapy by increasing tolerability, by decreasing side effects and therefore improving compliance. The benefit of such a strategy with regard to increasing eradication has been mixed. A reasonable amount of evidence now exists to suggest that supplementation of standard triple therapy with *Saccharomyces boulardii* is a useful adjunct. In a cohort of patients in Korea who received *S. boulardii* for 4 weeks during and after a 1-week course of standard triple therapy, eradication rates were 10% better than for those who did not receive the supplement [31]. A meta-analysis recently published illustrated that supplementation with *S. boulardii* significantly increased the eradication rate and reduced the risk of overall *H. pylori* therapy-related adverse effects especially diarrhea [32]. The effect of other probiotics is less well described. A study on *Lactobacillus acidophilus* revealed no real difference in eradication rates in patients with strains susceptible to both antibiotics, treated for peptic ulcer disease with standard triple therapy [33]. Similarly, a study on *Bifidobacterium*-containing yoghurt given with triple therapy failed to yield any increase in eradication although rates of non-diarrhea digestive side effects such as constipation and stomatitis were reduced [34]. A number of other adjuncts apart from probiotics have also been studied in the last year. One such adjunct is the powerful mucolytic agent erdosteine. This appears to be quite an efficient adjunct, and when used alongside a 14-day triple-therapy regime in a randomized, double-blind, placebo-controlled study, it improved eradication rates from 53 to 79% on a per-protocol analysis [35]. The antiulcer drug ecabet sodium has also been studied recently on patients undergoing second-line therapy with PPI, amoxycillin, and metronidazole and did not greatly improve eradication rates [36]. Further adjuncts may also emerge, and one such example may be citric acid, which was proven to have an anti-Helicobacter effect in vitro in a study published this year, although no clinical data are available to support this [37].

Proton Pump Inhibitors

It has been proposed that pretreatment with PPI decreases the efficacy of *H. pylori* eradication treatment. With so many patients being treated with PPI for a period prior to being investigated for dyspepsia, this could have obvious negative clinical implications. Two studies published on this topic this year, however, failed to support this hypothesis nor does it appear to have any impact on symptom severity and quality of life [38,39]. There is a cohort of patients, however, for whom the use of a PPI for *H. pylori* eradication might be undesirable, for instance those on dual antiplatelet therapy with coronary stents or patients with allergies and intolerances. A trial was published this year on a new-generation histamine-2 receptor antagonist, lafutidine, that has antisecretory properties. This study suggested that as part of a standard triple-therapy regimen, similar rates of eradication could be achieved with lafutidine as with lansoprazole with no increase in adverse events [40].

Individualization of Eradication Treatment

It may be possible to tailor the eradication regime offered to individual patients to maximize its efficacy. There are a number of options available to achieve this, which have been examined in the past such as examining bacterial virulence factors and pretesting for antibiotic susceptibility, but in the last year, some new developments have been made. One of the more interesting targets for this aim lies in understanding the role

of the cytochrome P450 2C19 (CYP2C19) genotype in *H. pylori* eradication. The effect here is exerted via the PPI component of therapy with polymorphisms of the CYP2C19 leading some individuals to metabolize more extensively than others. The studies carried out in the last year have mainly involved Chinese patients. One study divided subjects receiving a standard triple-therapy regime with omeprazole into extensive (EM), intermediate (IM), and poor (PM) metabolizers according to their CYP2C19 phenotype: 33% for the EM group, 92% for the IM group, and 100% for PM [41]. CYP2C19 polymorphisms can be overcome somewhat in EM by increasing PPI dose with one study showing significantly higher eradication rates in EM when 40 mg rather than 20 mg of omeprazole is used in a dual-therapy regime [42]. It may also be the case that not all PPIs are the same. In another Chinese study where esomeprazole was used, no significant difference was observed when 40 mg was used as opposed to 20 mg in either rate of eradication or side effects [43]. Similarly, in another study where rabeprazole and lansoprazole were used, a dose-dependent effect was not seen [44]. A study from Poland on Caucasian patients who use pantoprazole, however, found that carriage of the CYP2C19*2/*2 genotype was associated with treatment failures and that there were significant differences in measured pantoprazole concentrations based on genotype in a cohort of patients with peptic ulcer disease [45]. It should be noted that phenotype varies from region to region. Poor metabolizers (PM) encompass 2–4% of Caucasian and 14–20% of Asian populations, whereas extensive metabolizers make up a proportion of 18–27% in European populations but less frequently (1.3%) in Asians.

There are, of course, numerous other ways in which therapy can be individualized and tailored. In an increasingly globalized world, it may be the case that different treatments are appropriate for immigrant compared with native populations, which is quite plausible given that *H. pylori* is a latent infection usually acquired in childhood. A study from Italy this year showed statistically significant different levels of eradication in an indigenous versus immigrant population [46]. Age may also play a significant role with a recent Japanese study illustrating that younger patients have poorer eradication rates and tend to have a greater incidence of side effects [47]. A particular subset of patients may need individualized management of *H. pylori* infection based on comorbidity. It has been illustrated that eradication levels in patients with diabetes mellitus are lower than the general population. Trials published this year looked at using newer therapeutic regimes in this group. One study that examined the use of the sequential therapy in patients with type 2 diabetes yielded disappointing results with barely over 50% of patients achieving eradication [48]. Bismuth-based therapy appears to be more promising in this cohort, though, with a per-protocol eradication rate of 51% for patients with diabetes receiving triple therapy for 14 days compared with 85% for those receiving bismuth for the same duration [49].

Conclusion

The literature published pertaining to *H. pylori* eradication this year has shown a welcome bias toward a particular group of questions that pose challenges for clinicians. There has certainly been a greater emphasis on testing new alternatives to traditional triple therapy as first-line regimes. Still no ''magic bullet'' has emerged for *H. pylori* eradication, and the progress on a vaccine has also been frustratingly slow. Therapies based on levofloxacin and bismuth have long been reliable second-line treatments but may well be on the borderline of becoming the predominant first-line therapies. An advantage here may lie with the single-capsule preparation of bismuth-based therapy, which has the potential to reduce complexity and improve compliance. The value of compliance must not be understated and is the single biggest obstacle toward any eradication regime. It may also be compliance that determines whether sequential or ''concomitant'' regimens will be more useful. The complexity inherent in sequential therapy is considerably more than other eradication regimes, and this may limit its effectiveness. It is probably also fair to say that after a long period of uncertainty regarding probiotics, a useful role has now been established for *S. boulardii* as an adjunct to *H. pylori* eradication treatment. The third major field studied in the last 12 months has pertained to the individualization of therapy based on host polymorphisms, antibiotic resistance, demographic factors, and occasionally comorbidity. There is undoubtedly much more to be elucidated about the role of CYP2C19 and its interplay with PPIs. Indeed, this may be merely the tip of the iceberg as other polymorphisms may emerge in due course, which interact with the constituents of therapy. We propose that this copperfastens the need for national reference centers where information on all clinical and scientific aspects of *H. pylori* eradication can be collated and shared with international partners as we strive toward individualizing the most effective treatment to our patients.

Conflicts of Interest

The authors have declared no conflicts of interest.

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