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REVIEW: TREATMENT OF *HELICOBACTER PYLORI* INFECTION 2022

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Abstract – This review summarizes important studies regarding *Helicobacter pylori* therapy published from March 2021 to March 2022. Some of the major themes that emerge involve studies assessing the efficacy of high dose dual therapy regimens, the huge promise shown by vonoprazan as a component of eradication therapy and the use of personalised therapy. The nature of much of the work conducted over the last year has been dictated somewhat by the demands of the pandemic era, with far more systematic reviews and data syntheses and fewer original data on important factors such as resistance rates. Nonetheless, other studies have also been published which strengthen the importance of bismuth-based therapies, quadruple regimens and the use of novel tetracyclines and fluoroquinolones. A further body of work was undertaken on factors influencing the success and failure of therapies, all of which greatly enabling us to tackle the twin problems of antibiotic resistance and patient adherence to therapy.

Keywords: *H. pylori*, Treatment, Resistance, Compliance, Triple therapy, Bismuth.

INTRODUCTION

Compared to most of the last decade, this year has been a relatively fallow one in terms of the quantity of original research publications on the treatment of *Helicobacter pylori*, most likely reflecting the difficulty in undertaking clinical research in the midst of a global pandemic[1]. This was felt most keenly in the field of antibiotic resistance, with the attentions and efforts of many microbiology and infectious diseases departments being required elsewhere. In addition, the number of consensus guidelines was very low with meetings being very difficult to arrange. Two exceptions here were in Korea where a guideline emerged that endorsed standard triple therapy, concomitant therapy and sequential therapy for first line and bismuth-based therapy most strongly for second-line treatment, and in Spain where only quadruple therapies (with or without bismuth) and generally lasting 14 days, are recommended as first-line regimens[2,3]. That notwithstanding, the quality of research remains high and of an innovative and practical nature.

DUAL AND TRIPLE THERAPY AS A FIRST LINE TREATMENT

Given the longstanding concerns that the rates of eradication from standard triple therapy are falling, a number of data syntheses this year attempted to address this question. A very extensive network meta-analysis of randomised controlled trials (RCTs) concluded that standard triple therapy with proton pump inhibitors (PPIs) was the worst performing regimen but when vonoprazan was used, triple therapy was the only regimen that obtained eradication in more

than 90% ofs cases (92.5%), with levofloxacin-based therapy being the most efficacious in western countries, where vonoprazan has not been trialed (88.5% eradication)[4]. In this study, standard triple therapy had an overall efficacy of 75.7% consisting of 67.8% in western countries and 75.9% in east Asia. This regional variation was also seen in a meta-analysis and systematic review of 121 trials comprising 34,759 participants which looked at eradication rates from RCTs of first line therapies in various global regions, finding 14-day levofloxacin-based sequential therapy as the most efficient overall followed by modified bismuth-containing quadruple therapy for 10 days. Ten-day clarithromycin-based sequential therapy was the most efficacious in Africa, 14-day levofloxacin-based sequential therapy in Asia, and 14-day clarithromycin-based triple therapy in Europe, with North America generating insufficient data for network meta-analysis and in South America, none of the combinations were superior to the reference regimen[5].

As resistance rates and compliance are thought to be the two greatest obstacles to *H. pylori* eradication, in recent years the relatively simple concept of dual therapy with PPI and amoxicillin has grown in popularity. One study from China assessed eradication rates with a four times daily high dose dual therapy and found eradication rates of 85.8%, comparable with bismuth quadruple therapy, albeit lower rates were noted in smokers and overweight individuals[6]. Three systematic reviews were conducted on this dual therapy. The first showed that dual therapy had an identical eradication rate to mainstream first line therapies (90%) but with significantly fewer side effects, 8.70% *vs.* 22.38%[7]. Another meta-analysis[8] also reported 90% eradication for dual therapy, as compared to 85% for standard first line treatments. This data synthesis looked further at second line therapy and found dual therapy in this setting to be equal to standard guideline treatments. Again, an encouraging finding regarding tolerability and safety was observed with 19.6% reporting side effects with dual therapy compared to 36.7% with others but no difference in compliance. A further network meta-analysis, however, compared high-dose dual therapy (HDDT), bismuth-based quadruple therapy (BQT), sequential therapy (ST), concomitant therapy (CT) and hybrid therapy (HT) in the Asian population and again found HDDT to be the most effective regimen with the fewest side effects[9].

FLUOROQUINOLONES AS SECOND LINE TREATMENT

The use of fluoroquinolones with amoxicillin as salvage therapy in *H. pylori* eradication is a feature of the Maastricht V/Florence Consensus Report[10], although in recent years fluoroquinolone resistance has called this use into some question. A large study from a Taiwanese consortium investigated the efficacies of tetracycline-levofloxacin (TL) quadruple therapy and amoxicillin-levofloxacin (AL) quadruple therapy in the second-line treatment of *H. pylori* infection and had to be terminated after interim analysis due to clear superiority in favour of TL quadruple therapy (95% eradication) compared to AL quadruple therapy (69.6%), both including bismuth[11]. TL therapy remained quite efficacious even when levofloxacin-resistant strains were present (88.9%). In another trial aiming to increase options in the era of fluoroquinolone resistance, a novel fluoroquinolone antofloxacin was also trialled this year as part of a triple regimen in a group of 196 patients who had previously failed standard triple or BQT and yielded significantly superior eradication (87.6% *vs.* 68.5%) compared to levofloxacin based triple therapy with similar adverse event rates[12]. A similar study looked at antofloxacin and levofloxacin as components of BQT, again with superior eradication rates for the antofloxacin group (93.8%) compared to 86.2% in the levofloxacin group[13].

BISMUTH

Several studies this year assessed the various places where bismuth may be of use in *H. pylori* treatment. One RCT looked at ranitidine bismuth citrate (RBC) as a pre-treatment before standard triple therapy for *H. pylori* eradication and showed superior eradication in the pre-treatment group (80.9% *vs.* 67.3%), but was terminated early, due to a global safety concern regarding N-nitrosodimethylamine with ranitidine[14]. A more conventional, randomi-

sed, open-label trial conducted in Korea compared the efficacy of 10-day BQT with 7-day PPI-clarithromycin containing standard triple therapy (STT) as an empirical first-line therapy with the BQT group achieving a significantly higher eradication rate (74.3% versus 57.1%) albeit with poorer compliance and a higher rate of adverse events[15]. Numerous studies over the years have addressed various different antibiotic regimen components as part of bismuth based therapy. One such trial this year randomised patients to 12-day quadruple therapy regimens containing either tetracycline or furazolidone with the tetracycline group doing better at 87.1% eradication versus 83.9% with furazolidone, also with a significantly lower incidence of adverse events[16]. A systematic review comparing BQT and CT was conducted and yielded no difference of cure rate between BQT and CT (84.6% *vs.* 82.9%)[17]. A further study looked at modes of delivery of bismuth, which has been proposed as a way to address some concerns regarding the tolerability of bismuth, by comparing bismuth pectin capsules and bismuth pectin granules in the first-line quadruple treatment of *H. pylori*; however, there was no significant difference in eradication rate, symptom improvement rate, overall adverse reaction rate, or patient compliance[18].

SEQUENTIAL/CONCOMITANT/HYBRID/QUADRUPLE THERAPY

Original research on these therapies was sparse this year, however, a number of interesting data syntheses were published. One such systematic review of 24 trials including over 7,000 patients found CT to be superior to ST, particularly in the Asian setting even when only prescribed for 10 days compared to 14 days of ST, albeit with higher rates of adverse events[19]. Reverse hybrid therapy is a regimen that is proposed to combine the advantages of both CT and ST, using the same drugs but in reverse sequence, usually PPI plus amoxicillin and 2 other antibiotics for 7 days then PPI with amoxicillin alone for 3-7 days. A meta-analysis of four studies with 1,530 patients found a crude eradication rate of 95.5% with encouraging rates of 89% among clarithromycin resistant strains, 91% with metronidazole resistance and 86% for dual resistant strains[20]. Apart from these data syntheses, two interesting studies were completed in the Arab world. One such study on ST from Saudi Arabia reported very poor eradication rates of 63.4% for ST and 67.1% for STT, albeit with better cost-effectiveness for ST[21]. Another study in Syria compared doxycycline quadruple therapy with levofloxacin concomitant therapy with respective eradication rates of 76.9% and 82.1%[22].

PERSONALISED THERAPY

Personalised therapy guided by antibiotic susceptibility testing and host factors is growing in prominence. A meta-analysis conducted on 16 studies including nearly 5,000 patients found susceptibility-guided therapy to be superior to first-line clarithromycin-based triple therapy when clarithromycin resistance exceeded 20%[23]. Regarding host genetic factors a separate meta-analysis of 57 studies from 11 countries looked at the role of host genetics in treatment failure[24]. The bulk of the data and the most striking findings concerned the CYP2C19 polymorphism. This showed that enhanced vs poor metabolizer phenotypes were associated with a 2.52-fold significantly higher likelihood of eradication failure and a 4.44-fold significantly higher likelihood when treatment adherence and *H. pylori* clarithromycin susceptibility (if relevant) were confirmed. A separate meta-analysis of the same topic with an Asian focus found that *CYP2C19* polymorphism only influenced the *H. pylori* eradication rate in China and Japan and that rabeprazole-, esomeprazole- and pantoprazole-based regimens were not affected as much[25]. An intriguing prospective study examined the possibility that visual gene clip technology could be used to detect clarithromycin resistance and CYP2C19 status from gastric mucosal biopsies to guide the specific components of a 14-day BQT regimen[26]. Among the 242 patients who received tailored therapy, the *H. pylori* eradication rate was 91%. Other studies, however, demurred from the enthusiasm for susceptibility-based therapy. One group studied 490 *H. pylori*-positive patients retrospectively and found the eradication rate in a group where treatment was tailored based on clarithromycin susceptibility testing to be 87.8% compared to 91.8% in an empirical BQT

group, with the latter experiencing fewer adverse events and lower costs of care[27]. Another published meta-analysis of 48 studies found 95% of patients with supposedly susceptible strains but only 63.4% of those patients achieved good eradication rates, again suggesting the importance of adherence to therapy[28].

THE BARRIERS TO TREATMENT SUCCESS: COMPLIANCE AND RESISTANCE

It is widely accepted that the two greatest challenges in optimising treatments for *H. pylori* are improving patient compliance and overcoming antimicrobial resistance. Regarding compliance, it is of crucial importance that patients are adequately educated and informed on the components of their *H. pylori* eradication treatment which can be complex, with benefits to the patient that may not be immediately apparent. A meta-analysis of Enhanced Patient Education (EPE) programmes found that these led to markedly improved adherence to therapy and eradication rates[29]. In China, an initiative to use a social media platform to provide patients with education, support and encouragement during their therapy period led to an eradication rate of 90% compared to 77% in controls[30]. A systematic review was conducted this year where enhanced patient instructions (EPI) used methods such as telephone-based re-education, short-message service, and WeChat[31]. It was noted that compared with patients receiving only regular instructions, patients receiving EPI showed significantly higher *H. pylori* eradication rates (RR = 1.20) and better patient compliance (RR = 1.23), as well as higher patient satisfaction (RR = 1.42). A similar meta-analysis with some overlap of technology-enhanced communication (TEC) strategies also found that such initiatives significantly improved patient compliance (OR 4.52) and eradication rate (OR 1.98)[32].

As microbiologists around the world struggled with an unprecedented challenge during the pandemic it is perhaps unsurprising that there were comparatively few studies published on *H. pylori* resistance rates. One significant meta-analysis from a region not previously well studied was conducted on resistance rates in Australia and New Zealand over the last 20 years and showed a more than doubling of clarithromycin resistance, from 7.4% to 16.1%, with stable rates of resistance to metronidazole, fluoroquinolone, amoxicillin and tetracycline in that time frame[33]. The individual studies detailing resistance are summarised in Table 1[33-40]. Finally, an interesting meta-analysis reported on the phenomenon of heteroresistance,

TABLE 1. *HELICOBACTER PYLORI* RESISTANCE TO ANTIBIOTICS IN THE STUDIES PUBLISHED DURING THE LAST YEAR WORLDWIDE.

Author	N	Region	AMO %	CLA %	MET %	QUINOLONE %	TET %	RIF %
Schubert[33]*	1810	Australia & New Zealand	2.1	16.1	50.5	(ALL) 2.9	0.3	-
Hallur[34]	93	India	3.1	34.4	81.2	(LVX) 65.6	-	-
Tian[35]	180	China	15.1	25.5	96.4	(LVX) 67.3	-	-
Vanden Bulcke[36]	512	Belgium	2.7	13.5	29.7	(LVX) 29.7	0.0	11.4
Ho[37]*	2660	USA	2.6	31.5	42.1	(LVX) 37.6	0.9	0.2
Nestegard[38]	50	Norway	-	11	38	-	12	-
Azadbakht[39]	205	Iran	46.8	70.7	33.2	(LVX) 36.1	41	-
Li[40]	54	China	18.5	50.0	77.8	(LVX) 33.3	13	-

*Meta-analysis AMO = Amoxicillin, CLA = Clarithromycin, MET = Metronidazole, TET = Tetracycline, RIF = Rifabutin, LVX = Levofloxacin.

i.e., the presence of resistant and susceptible *H. pylori* populations in the same sample and/or a difference in the susceptibility patterns between biopsy samples[41]. The analysis of 22 studies that had investigated 3,852 H. *pylori* positive patients found 6.8% heteroresistance to clarithromycin and 13.8% to metronidazole.

ACID INHIBITION – PROTON PUMP INHIBITORS AND POTASSIUM COMPETITIVE ACID BLOCKERS

Vonoprazan, the first potassium competitive blocker (P-CAB) has again been the subject of much interest in the field of *H. pylori* eradication with consistently strong results in recent years. A study from Thailand showed eradication rates of 96.7% for 7-day vonoprazan triple therapy compared to 88.5% for a 14-day course of STT[42]. However, the results of vonoprazan were not quite as impressive when used as part of a dual therapy, with rates of 66.7% for 7 days of treatment and 89.2% for 10 days[43]. A second P-CAB, tegoprazan, underwent a pharmacokinetic and pharmacodynamic study when co-administered with amoxicillin/clarithromycin in healthy subjects and illustrated a more favourable gastric pH profile for the agent compared to pantoprazole[44]. Continuing on the theme of PPIs, a further meta-analysis concluded that for the triple therapy regimen of PPI- clarithromycin-metronidazole, and the common practice of using PPIs prior to eradication therapy were associated with higher rates of eradication, albeit not for other regimens[45].

OTHER ANTIBIOTIC TRIALS

Data emerged on several other antibiotics used as part of *H. pylori* eradication treatments this year. Regarding furazolidone, in a high clarithromycin resistance region, furazolidone-based BQT achieved 92% eradication compared to 88% for clarithromycin and was seen to have superior cost-effectiveness and acceptable safety[46]. Doxycycline is another agent considered to be capable of overcoming resistance challenges. A meta-analysis was therefore conducted on doxycycline and minocycline as part of eradication treatment, looking at 23 studies and over 5,000 patients. It was noted that when these synthetic tetracyclines were used as part of triple therapy, the eradication rates were less than 75% compared to 95% in quadruple therapies[47]. Yet another systematic review examined rifabutin as part of both first-line and rescue therapies; it showed a severe lack of studies on the agent as part of first line therapy compared with conventional treatment controls, with just one study on first line therapy. For all uses, it was noted that treatment was more likely to be successful in Asian versus non-Asian populations (81.0% *vs.* 72.4%) with an overall rate of 24.8% for adverse events[48].

PROBIOTICS AND OTHER ADJUNCTS TO THERAPY

For many years now probiotics have been studied as a means of improving *H. pylori* eradication rates. The proposed mechanisms for this include a direct anti-*H. pylori* effect and also the possibility that co-prescription of probiotics while people are on therapy will reduce the side effects associated with therapy and thereby improve adherence. Lactobacilli have been the most frequently studied agents and several studies emerged from Asia this year to shed more light on this topic. One study looked at the role of non-viable *Lactobacillus reuteri* DSM17648 combined with 14-day STT on *H. pylori* eradication, and although eradication rates were not improved (81%), supplementation helped to build up a beneficial microbial profile and reduced the frequencies of abdominal distention, diarrhoea, and the Gastrointestinal Symptom Rating Score, possibly via an effect on any concurrent irritable bowel syndrome[49]. Other studies looked at Lactobacilli in combination with other adjuncts. A Taiwanese paper looked at the role of *Lactobacillus rhamnosus* on the bacterial load and found that the agents significantly decreased the number of organisms and modified the gut microbiota, although no eradications were observed in the RCT of 40-patients[50]. In Iran, a double-blind RCT was conducted comparing treatment with *Lactobacillus reuteri* and *Saccharomyces boulardii* and

found both to be superior to the non-probiotic arm (92.3% and 94.2% respectively, compared to 86.5% for the controls), but with only the *S. boulardii* group reaching statistical significance both in terms of eradication and in reducing side effects[51].

A number of probiotic studies were also conducted in Europe. In Turkey, a study of 400 patients showed significantly increased efficacy when bovine lactoferrin was added to both STT and ST, with a 10-day ST plus lactoferrin reaching the highest eradication rate of 94.5%[52]. A further probiotic study from a Greek group looked at the addition of a four strain containing probiotic (*Lactobacillus acidophilus*, *Lactiplantibacillus plantarum*, *Bifidobacterium lactis,* and *S. boulardii)* along with a 10-day concomitant non-bismuth quadruple *H. pylori* eradication regimen. The results of this trial were encouraging with an increase in eradication rate from 86.8% to 92% noted in the probiotic group, as well as a markedly reduced incidence of side effects (17% *vs.* 51%)[53].

In a South American cohort, the addition of S. *boulardii* CNCM-I 745 to the conventional antibiotic eradication therapy for *H. pylori* reduced the number of antimicrobial resistance genes (ARGs) in the faeces compared to the standard of care[54].

As well as probiotics, a few other treatment adjuncts were studied this year. An Egyptian study found that vitamin D supplementation to a 14day STT was associated with increased eradication rates ranging from 61% to 80%[55]. The effect of periodontal treatments in eradicating *H. pylori* has long been discussed and this year a systematic review and meta-analysis conducted on the topic found that the addition of a periodontal treatment resulted in improvement in gastric *H. pylori* eradication rates with an OR of 4.11 and non-recurrence rates with an OR of 5.36[56].

EFFECT OF H. PYLORI ERADICATION ON THE MICROBIOTA

Further data have accrued this year on the effect of *H. pylori* eradication on the microbiota. One study showed that after eradication the gastric microbiota was significantly disrupted in young adults, and this could not be restored in a short time[57]. When probiotics were used to supplement eradication treatment, the microbial diversity was closer to that of *H. pylori*-negative patients compared to the standard quadruple therapy group. *H. pylori* eradication therapy alters gut microbiota, provoking gastrointestinal symptoms that could be improved by probiotics. A study from Germany assessed the effect of fermented milk, containing yogurt and *Lacticaseibacillus* (*L. rhamnosus and L. paracasei),* on *H. pylori* positive patients and found that, following *H. pylori* treatment, there was a significantly faster recovery of the microbiota composition (beta-diversity) and short chain fatty acid production as well as a limited increase in potentially pathogenic bacteria[58]. A meta-analysis of studies looking at the effect of eradication treatment on the gastric microbiota found that successful *H. pylori* eradication could reverse the gastric microbiota dysbiosis and show beneficial effects, potentially providing new insight for exploring the role of *H. pylori* and the whole gastric microbiota in gastric carcinogenesis[59].

FACTORS INFLUENCING SUCCESS OF TREATMENT

Several other interesting articles emerged this year looking at tangential factors that may influence treatment success or failure. One comprehensive meta-analysis of the effect of *H. pylori* eradication on diabetes mellitus examined 36 studies and found that, while the risk of treatment failure was higher in diabetic patients (OR = 2.59), successful eradication improved glycaemic control[60]. Another meta-analysis looked at the role of smoking and found that, overall in 39 studies, smoking increased the failure rate of *H. pylori* eradication treatment (OR = 1.70) rising to an OR of 2.59 when the number of cigarettes per day was increased by more than five[61]. A further meta-analysis looking at the phenomenon of recurrence and recrudescence found an annual rate of 4%, and a stable trend with the time elapsed after eradication[62]. A systematic review and meta-analysis of 12 studies found the eradication rate of whole-family treatment was higher (OR=2.93) and recurrence rate was lower (OR=0.3)[63]. Physician factors are also at play. A study of Chinese physicians found 26.5% of respondents indicating that their hospitals had dedicated clinics for managing *H. pylori* infection, with 91.0% of respondents having routinely

recommended a reexamination 1 to 2 months after eradication therapy, and 95.1% were advised to stop PPI treatment at least 2 weeks before re-examination. The authors concluded that the physician's skills and knowledge concerning the diagnosis and treatment of *H. pylori* infection could be improved[64].

CONCLUSIONS

Many studies pertaining to *H. pylori* eradication treatment were found in the published literature over the last 12 months, across a diversity of topics, although several broad themes emerged. Given the extenuating circumstances of the last 2 and a half years, much of the literature was in the form of data synthesis. This particular modality, in fact, may be considered to be at a crossroads in the *H. pylori* treatment field, as criticism emerged this year that the information coming from them is undermined by problems such as the poor quality of the clinical trials using non-optimised regimens and incomparable comparisons related to marked geographic and ethnic genotypic and phenotypic heterogeneity[65].

The concept of high dose dual therapy with PPI, if not vonoprazan, and amoxicillin has certainly produced robust data this year and is likely to grow in popularity. Regarding fluoroquinolones, the novel agent antofloxacin may offer some promise as a means of dealing with rising levofloxacin resistance. Personalised therapy continues to offer an attractive emergent means of prescribing effective therapy, although it remains to be seen what the exact advantage will be in terms of eradication therapy over existing empirical regimens. As ever, the biggest barriers to treatment success remain patient compliance and antimicrobial resistance, and the promise shown by various patient education and compliance support platforms may help with this. Vonoprazan is, in many ways, the most exciting new drug to emerge for *H. pylori* eradication in a long time and further validation studies outside Asia are awaited with interest.

Conflict of Interest

The authors declare no conflict of interest.

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