What are the global response rates to *Helicobacter pylori* eradication therapy?

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C Nash, L Fischbach, S Veldhuyzen van Zanten. What are the global response rates to *Helicobacter pylori* eradication therapy? Can J Gastroenterol 2003;17(Suppl B):25B-29B.

OBJECTIVE: To perform a systematic review of the world literature to determine current success rates of *Helicobacter pylori* eradication treatment.

METHODS: Computer searches were performed to identify systematic reviews or meta-analyses of treatment studies of *H pylori* infection. The searches included specifications for Asia, Africa, North America, South America and Europe.

RESULTS: The data supported the current worldwide recommendation to use proton pump inhibitor (PPI)-based triple therapy with clarithromycin and either metronidazole or amoxicillin. There are, however, regional differences in success rates that are not completely explained by resistance to either metronidazole or amoxicillin. For second-line therapy, quadruple therapy using a PPI with bismuth, metronidazole and tetracycline (PPI-BMT) is superior to an alternative PPI-based triple therapy.

CONCLUSION: There is worldwide consensus that PPI-based triple therapy, preferably with clarithromycin and amoxicillin or clarithromycin and metronidazole, is used as first-line therapy. Quadruple therapy of PPI-BMT is the preferred rescue medication after initial failure of therapy.

Key Words: Antibiotic resistance; *Helicobacter pylori*; Meta-analysis; Review; Treatment

In this paper, we discuss a systematic review of the literature, which was performed to answer the question of the current worldwide success rates of *Helicobacter pylori* eradication treatment. The effect of resistance to antibiotics, especially metronidazole and clarithromycin, on treatment effectiveness was also assessed.

IDENTIFICATION OF RELEVANT STUDIES

A systematic review of the English literature from 1985 until September 2002 was performed using PubMed. Searches focussed on identifying systematic reviews or meta-analyses of *H pylori* eradication treatments. Where necessary, data from individual studies were also evaluated. The following subject headings were used: eradication, treatment, Asia, Africa, North America, South America, Europe, antimicrobial resistance, metronidazole, and clarithromycin. We evaluated the literature, which examined treatment effectiveness worldwide,

Quel est le taux de réponse mondial à la thérapie d'éradication de l'*Helicobacter pylori*?

OBJECTIF DE L'ÉTUDE : Procéder à une analyse systématique de la documentation médicale mondiale pour déterminer le taux de succès courant du traitement d'éradication de l'*Helicobacter pylori*.

MÉTHODOLOGIE : Des recherches informatiques ont été exécutées pour repérer les analyses systématiques ou les méta-analyses des études des traitements de l'infection à *H pylori*. Les recherches incluait des paramètres pour l'Asie, l'Afrique, l'Amérique du Nord, l'Amérique du Sud et l'Europe.

RÉSULTATS : Les données étayaient la recommandation mondiale courante d'utiliser la trithérapie incluant un inhibiteur de la pompe à protons (IPP) accompagné de clarithromycine et de métronidazole ou d'amoxicilline. Cependant, on remarque des différences régionales pour ce qui est des taux de succès, lesquelles ne s'expliquent pas entièrement par une résistance au métronidazole ou à l'amoxicilline. Comme traitement de deuxième ligne, une quadrithérapie faisant appel à un IPP avec du bismuth, du métronidazole et de la tétracycline (IPP-BMT) est supérieure à une autre trithérapie à l'IPP.

CONCLUSION : Il existe un consensus mondial sur l'utilisation d'une trithérapie à l'IPP, accompagnée de préférence de clarithromycine et d'amoxicilline ou de clarithromycine et de métronidazole, comme traitement de première ligne. La quadrithérapie d'IPP-BMT est le médicament de rattrapage favorisé lorsque le premier traitement échoue.

compared treatments within or across studies, and evaluated the effects of antibiotic resistance, treatment duration and drug dosing on treatment success.

RESULTS

Two meta-analyses were identified that specifically reviewed worldwide cure rates for treatments to eradicate *H pylori* infection (1,2). One of the most comprehensive reviews was the meta-analysis by Fischbach et al (1), which evaluated 618 different treatment groups. The aim of this paper is to provide data on worldwide eradication rates. However, as identified by Fischbach et al (1), most of the studies were carried out in Western Europe, North America and Northeast Asia. Specifically, 66% of studies were performed in Western Europe, 11% in the United States and Canada, and 9% in Northeast Asia. Only 3% of studies were performed in South America and 1% in Africa (1). It is clearly difficult to make definitive state-

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ments about success rates of treatment in the latter two areas.

A large number of studies evaluating *H pylori* eradication treatment have small sample sizes. In the Fischbach et al review (1), 17% of studies enrolled less than 50 patients. In the meta-analysis by Laheij et al (2), the median sample size of studies was 30 patients. Only 50% of studies used any form of randomization and only 7% were placebo controlled (1). Most studies evaluated duration of treatment for seven to 13 days (47%) or for more than 14 days (49%). Only 4% of studies evaluated treatment duration of less than seven days (1). For nitroimidazole-based regimens, treatment for seven to 13 days was 5.9% less effective than 14-day treatments (1). It was clear that treatment given for less than seven days was sub-optimal with only a 33% eradication rate (1).

An important role of a meta-analysis is to identify sources of systematic variation across studies (3). Indeed, in 12 of the 16 main treatments evaluated by Fischbach et al (1), heterogeneity in treatment effectiveness was identified. Identified sources of heterogeneity can reveal conditions under which treatments are most effective and when they are not. In the meta-analysis by Fischbach et al (1), predictors of nitroimidazole-based *H pylori* eradication treatment failure included high levels of nitroimidazole resistance and high *H pylori* transmission rates. High *H pylori* transmission rates are more frequently seen in countries of low socioeconomic development that have a high prevalence of *H pylori* infection. Outside of northeastern Asia, the *H pylori* cure rate for nitroimidazole-based regimens decreased by 0.5% for every 1% increase in the prevalence of metronidazole resistance (1). However, nitroimidazole-based regimens were more successful in northeastern Asia, irrespective of the prevalence of metronidazole resistance (1).

In a meta-analysis evaluating the effect of resistance to metronidazole and clarithromycin, Dore et al (4) found that the presence of metronidazole resistance reduced the efficacy of eradication treatment by 38%. Methodological differences might explain why these results differ from the findings of Fischbach et al (1). For instance, in the analysis by Fischbach et al (1), the effect of metronidazole resistance was assessed independent of geographic location, such as northeastern Asia, and included estimates of metronidazole resistance from

within the study and from published estimates of the prevalence of metronidazole resistance in the source population. Clarithromycin resistance reduced effectiveness by an average of 55% (4). The study by Dore et al (4) also found heterogeneity for the data involving metronidazole-containing regimens.

There is marked variability in the prevalence of metronidazole resistance in different geographic regions (1,5). The problem is confounded by the difficulty of separating metronidazole-sensitive from resistant *H pylori* strains. In contrast to clarithromycin, where there is a definite bimodal distribution separating sensitive from resistant strains, there is a much wider range of minimal inhibitory concentration values for metronidazole, making the definition of resistance more ambiguous (6).

Use of nitroimidazoles

Given the importance of metronidazole resistance as a predictor of treatment failure, why do nitroimidazole-containing regimens continue to be used, even in populations where the prevalence of metronidazole resistance has increased over time (7)? The large MACH-2 study (8) illustrated that metronidazole is a very potent antibiotic against *H pylori* infection. The dual combination of clarithromycin and metronidazole (CM) achieved a 69% success rate compared with only 25% for the dual combination of clarithromycin and amoxicillin (CA). When omeprazole was added to the dual combinations (OCM and OCA, respectively), the cure rates were comparable: 91% and 95%, respectively (8). Other studies have consistently shown improved effectiveness when a nitroimidazole was added to a non-nitroimidazole-based dual therapy (9-18) (Table 1). Metronidazole is, therefore, an active antibiotic against *H pylori* infection.

Characteristics of proton pump inhibitor-based triple therapies

All currently available proton pump inhibitors (PPIs) (esomeprazole, lansoprazole, omeprazole, pantoprazole, and rabeprazole) appear to be equally effective when given with CA or CM. The overall success rate reported in clinical trials ranges from 59% to 100% (1,2,19-25). Most studies evaluated

TABLE 1
Intervention trials comparing the effectiveness of non-nitroimidazole-based anti-*Helicobacter pylori* dual treatment regimens with the same regimen with an added nitroimidazole

Author, country, year	Study design	Dose (mg)/frequency/duration			% of subjects with <i>H pylori</i> eliminated after treatment*	
		Dual therapy	Nitroimidazole	Dual therapy without nitroimidazole	With nitroimidazole added	
Chiba, Canada, 1996 (9)	RCT	C 250/bid/2 wks; O 20/bid/2 wks	M 500/bid/2 wks	19/30 (58%)	29/32 (91%)	
Goh, Malaysia, 1994 (10)	RCT	A 500/tid/2 wks; O 40/day/2 wks	M 200/qid/2 wks	15/19 (79%)	19/22 (86%)	
Koizumi, Japan, 1998 (11)	RCT	A 500/tid/2 wks; O 20/day/8 wks	M 500/bid/2 wks	13/25 (52%)	20/23 (87%)	
O'Riordan, Ireland, 1990 (12)	Intervention	A 500/tid/1 wk; CBS 120/qid/4 wks	M 400/tid/1 wk	9/18 (50%)	23/31 (74%)	
Pilotto, Italy, 1996 (13)	RCT	A z 500/day/3 days; O 20/day/2-4wks	M 250/qid/1 wk	7/16 (44%)	10/18 (56%)	
		C 250/bid/1 wk; O 20/day/1 wk	M 250/qid/1 wk	9/18 (50%)	17/19 (89%)	
Saberi-Firoozi, Iran, 1995 (14)	RCT	A 500/qid/2 wks; O 40/bid/2 wks	Ti 500/bid/2 wks	16/46 (35%)	25/43 (58%)	
Sant, Ireland, 1992 (15)	Intervention	A 500/tid/1 wk; CBS 120/qid/4 wks	M 400/tid/1 wk	9/18 (50%)	31/36 (86%)	
Stack, UK, 1998 (16)	RCT	C 500/bid/1 wk; R 20/bid/1 wk	M 400/bid/1 wk	12/21 (63%)	18/19 (95%)	
Tursi, Italy, 1996 (17)	Intervention	A 1000/bid/2 wks; O 20/bid/2 wks	Ti 500/bid/2 wks	23/39 (59%)	24/28 (86%)	
Wong, China, 2000 (18)	RCT	A 1000/bid/2 wks; L 30/bid/2 wks	M 500/bid/2 wks	43/75 (57%)	68/82 (83%)	

*Proportion of subjects evaluated post-treatment. A Amoxicillin; Az Azithromycin; bid Twice per day; C Clarithromycin; CBS Colloidal bismuth citrate; Day Once a day; M Metronidazole; O Omeprazole; qid Four times per day; R Rabeprazole; RCT Randomized clinical trial; Ti Tinidazole; tid Three times per day; wk Week

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a seven-day treatment duration. There are too few head-to-head studies available in the literature to make definitive statements about the optimal duration of treatment. In a meta-analysis evaluating 13 studies using PPI-CA of various durations, it was found that 10- or 14-day regimens were 7% to 9% more effective than a seven-day regimen (26).

Most regional consensus statements have advocated a seven-day PPI-based triple therapy as the first choice. The major exception has been in the United States, where 10-day treatment has been recommended. In the United States, a 14-day PPI-AC regimen tended to perform better than the seven-day regimen (92% versus 86%) (1). However, a recent large randomized trial carried out in the United States did not confirm an improved efficacy for a 10-day PPI-AC treatment. In the study reported by Vakil et al (27) involving 807 patients, the PPI rabeprazole was evaluated together with clarithromycin and amoxicillin (RAC) given for three, seven or 10 days, and compared with OAC given for 10 days. The success rate for the seven-day RAC regimen was 77% compared with 78% for RAC and 73% for OAC, each given for 10 days. This study did not support the duration of 10 days that is currently recommended in the United States.

Dose of metronidazole: The optimal dose of metronidazole in PPI-CM is not known. The MACH studies (8), which established PPI-CM as a first-line treatment, used a metronidazole dosage of 400 mg twice daily, which is the standard dosage recommended in Europe. In other areas, metronidazole 500 mg twice daily appears to be most commonly used. Evidence is lacking as to whether higher doses of metronidazole might improve efficacy in PPI-CM regimens. Higher dosages of metronidazole have resulted in higher efficacy with the generally less efficacious regimen of amoxicillin, metronidazole, and PPI (PPI-AM). In one study (28), there was a trend for higher dosages of metronidazole (1600 mg daily) to overcome metronidazole resistance when compared with metronidazole 400 mg twice daily.

Dose of clarithromycin: A recent meta-analysis evaluated the dose of clarithromycin when used in the PPI-CA combination (29). It showed that PPI-CA using 500 mg clarithromycin twice daily gave an 87% eradication rate, which was significantly better than PPI-AC using a clarithromycin dose of 250 mg twice daily, which achieved a 78% eradication rate. This finding was also confirmed in head-to-head studies. In the same study, no difference was found when a clarithromycin dosage of 500 mg twice daily was compared with a dosage of 250 mg twice daily when used in the PPI-CM combination (29); the cure rates were 88% and 87%, respectively. Although these meta-analyses support the current recommended doses of clarithromycin in PPI-CA and PPI-CM, it is interesting that a total daily dose of clarithromycin of 1.5 g gave statistically significantly better results for both PPI-CA and PPI-CM in the meta-analysis reported by Laheij et al (2). However, the study did not provide information to further quantify how much more successful treatments were.

Use of bismuth compounds

Bismuth compounds have proven efficacy against *H pylori* infection (30) especially in some populations of Asia, Europe and North America when used in triple or quadruple therapies with a nitroimidazole and either tetracycline or amoxicillin (1). The most commonly used compounds are bismuth subsalicylate (BSS) and colloidal bismuth subcitrate (CBS). The

third compound is ranitidine bismuth citrate (RBC). Interestingly, for all three compounds, the exact chemical structure is not known (31). To date, RBC has been the only marketed drug that was developed specifically for treatment of *H pylori* infection. However, due to low physician demand, this drug has been removed from most markets. This is unfortunate because there are good data demonstrating that the triple combination of RBC-CA or RBC-CM performed as well as the PPI-CA and PPI-CM combinations. In systematic reviews, the efficacy of the combination of RBA-CA was found to be equivalent to that of PPI-CA (19,20). However, RBC-CM triple therapy may be slightly more effective than PPI-CM because the pooled cure rates for RBC-CM were slightly higher than PPI-CM: 87% compared with 75% in head-to-head studies (19). Although not all of the five studies evaluated in the review by Gilbert et al (19) assessed metronidazole resistance, there was a suggestion that RBC-CM can partially overcome the effect of metronidazole resistance.

Recently it has been suggested that CBS may also be withdrawn from the market. However, a new bismuth triple formulation in a single tablet has been developed recently and appears to have excellent efficacy (32,33).

The most commonly used PPI-based quadruple therapy is a PPI with bismuth, metronidazole and tetracycline (PPI-BMT). When successful, this treatment is most commonly given as follows: PPI twice daily; bismuth (120 mg as two tablets of BSS or one tablet of CBS) four times daily; metronidazole 200 mg, 250 mg, 400 mg or 500 mg three to five times daily; and tetracycline 500 mg four times daily. Several meta-analyses support the conclusion that, as a first-line therapy, PPI-BMT quadruple therapy is as efficacious as the recommended PPI-CA or PPI-CM triple therapies and achieves eradication in 75% to 85% of cases. (1,2). The drawback of quadruple therapy is that it is cumbersome and requires dosing four times daily for a total of 18 to 22 tablets daily. This has, in part, been overcome by the new single capsule triple therapy (32).

Consensus about first-line treatment

There is consensus worldwide that triple therapy consisting of a PPI together with clarithromycin and either amoxicillin or metronidazole should be considered first-line treatment for the eradication of *H pylori* infection (34-37). These consensus statements were made notwithstanding heterogeneity in treatment results and in spite of the fact that treatment had sometimes not yet been adequately tested in the population that was targeted for the regional consensus report (1). For clarithromycin, the standard dosage is 500 mg twice daily when given with amoxicillin 1 g twice daily. For PPI-CM, the clarithromycin dosage generally is 250 mg twice daily and metronidazole 400 mg to 500 mg twice daily. There is evidence that giving the PPI twice daily is better than once daily (38). More recently, PPI-CA triple therapy has emerged as the first choice over PPI-CM because PPI-CA is not dependent on the prevalence of metronidazole resistance, which varies markedly among regions. Another reason is that if first-line treatment fails, a metronidazole-based regimen can still be used as second-line therapy without the risk that secondary metronidazole resistance would be induced by the first-line therapy (34).

Second-line therapies

In general, current first-line therapies have heterogeneous efficacy (1). It is likely that the efficacy of existing first-line ther-

apies will be lower when used in a community-based setting. The suggested approach for second-line therapy is to either switch to an alternative PPI-based triple therapy or to use PPI-BMT quadruple therapy. There is reasonable evidence to recommend PPI-BMT quadruple therapy. Success rates are higher if 500 mg of metronidazole four times daily is used rather than 250 mg four times daily (39), and it is superior to an alternative PPI-based triple therapy (39-41). In a recent meta-analysis (39), the overall success rate for the PPI-BMT second-line therapy was 76% compared with 70% for PPI-CA or PPI-CM. One explanation for this may be that quadruple PPI-BMT therapy is better able to overcome metronidazole resistance than PPI-CM. For example, one review showed that while the success rate for PPI-BMT and PPI-CM given for seven days was 94% in the metronidazole-sensitive strains, PPI-BMT was successful in 83% of patients harbouring metronidazole-resistant strains compared with 73% of patients given PPI-CM (5).

Geographic differences

The reason for geographic differences in metronidazole-resistance remains unclear. Frequent use of metronidazole in countries with a high prevalence and, hence, high transmission rate of *H pylori* infection has been identified as a risk factor (1,5). This occurs in countries with low socioeconomic development and poor sanitation. In such countries, the incidence of diarrheal illness, which is often treated with metronidazole, is also high. Frequent use of metronidazole, especially in populations where it is available without a prescription, will likely lead to an increase in the prevalence of metronidazole-resistant strains of *H pylori* (42).

A detailed description of variations in prevalence rates in different regions is beyond the scope of this article. However, even in a country like the United States, marked differences in prevalence are found in different regions (43). Resistance rates to clarithromycin vary from 3.4% to 11.5% and to metronidazole from 29% to 40% (43).

Northeastern Asia warrants special mention. In the meta-analysis by Fischbach et al (1), nitroimidazole-based regimens in northeastern Asia were, on average, 10% more effective than in other regions of the world. As stated previously, this higher eradication rate was independent of the prevalence of metronidazole resistance in the region. The reasons for this are unclear. Finally, it should be noted that the eradication rate of PPI-based triple therapies appears to be lower in Latin America (1, 44). In this region, good results are also obtained with furazolidone-based triple therapy, especially when a PPI is combined with amoxicillin or clarithromycin and furazolidone (45). The most successful regimen in developing countries outside of northeastern Asia was the two-week triple therapy of clarithromycin and amoxicillin with a PPI (93%; 95% CI 92 to 95) (unpublished data, Lori Fischbach).

CONCLUSIONS

PPI-based triple therapies with clarithromycin and either amoxicillin or metronidazole in most areas of the world have been adopted as first-line treatments for the eradication of *H pylori* infection. Increasingly, PPI-CA is favoured over PPI-CM because of varying but generally high rates of metronidazole resistance and because the use of PPI-CA avoids induction of secondary resistance to metronidazole. There are still uncertainties about the optimal duration of treatment, but generally seven-day treatment is most commonly used. There is reasonable evidence to indicate that for second-line therapy, PPI-BMT quadruple therapy is superior to PPI-based triple therapies. Further studies are needed to determine what the optimal dosage of antibiotics is when given in PPI-based triple therapy or in quadruple therapy. There is clearly room for novel treatments to improve the overall success rates of eradication treatment. There is also a need for additional testing of *H pylori* eradication treatments in the previously overlooked developing world, where most *H pylori* infections occur.

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