Indications for treatment of *Helicobacter pylori* infection: a systematic overview

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Objective: To determine (a) the advantages and disadvantages of treatment options for the eradication of *Helicobacter pylori* and (b) whether eradication of *H. pylori* is indicated in patients with duodenal ulcer, nonulcer dyspepsia and gastric cancer.

Data sources: A MEDLINE search for articles published in English between January 1983 and December 1992 with the use of MeSH terms *Helicobacter pylori* (called *Campylobacter pylori* before 1990) and duodenal ulcer, gastric cancer, dyspepsia and clinical trial. Six journals and *Current Contents* were searched manually for pertinent articles published in that time frame.

Study selection: For duodenal ulcer the search was limited to studies involving adults, studies of *H. pylori* eradication and randomized clinical trials comparing anti-*H. pylori* therapy with conventional ulcer treatment. For nonulcer dyspepsia with *H. pylori* infection the search was limited to placebo-controlled randomized clinical trials.

Data extraction: The quality of each study was rated independently on a four-point scale by each author. For the studies of duodenal ulcer the outcome measures assessed were acute ulcer healing and time required for healing, *H. pylori* eradication and ulcer relapse. For the studies of nonulcer dyspepsia with *H. pylori* infection the authors assessed *H. pylori* eradication, the symptoms used as outcome measures and whether validated outcome measures had been used.

Data synthesis: Eight trials involving duodenal ulcer met our inclusion criteria: five were considered high quality, two were of reasonable quality, and one was weak. Six trials involving nonulcer dyspepsia met the criteria, but all were rated as weak. Among treatment options triple therapy with a bismuth compound, metronidazole and either amoxicillin or tetracycline achieved the highest eradication rates (73% to 94%). Results concerning treatment indications for duodenal ulcer were consistent among all of the studies: when anti-*H. pylori* therapy was added to conventional ulcer treatment acute ulcers healed more rapidly. Ulcer relapse rates were dramatically reduced after *H. pylori* eradication. All of the studies involving nonulcer dyspepsia assessed clearance rather than eradication of *H. pylori*. No study used validated outcome measures. A consistent decrease in symptom severity was no more prevalent in patients in whom the organism had been cleared than in those taking a placebo. Of the studies concerning gastric cancer none investigated the effect of eradication of *H. pylori* on subsequent risk of gastric cancer.

Conclusions: There is sufficient evidence to support the use of anti-*H. pylori* therapy in patients with duodenal ulcers who have *H. pylori* infection, triple therapy achieving the best results. There is no current evidence to support such therapy for nonulcer dyspepsia in patients with *H. pylori* infection. Much more attention must be paid to the design of nonulcer dyspepsia studies. Also, studies are needed to determine whether *H. pylori* eradication in patients with gastritis will prevent gastric cancer.

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← For prescribing information see page 264

Objectif : Déterminer a) les avantages et les inconvénients des traitements possibles pour éliminer l'*Helicobacter pylori* et b) si l'éradication du *H. pylori* est indiquée chez les patients atteints d'ulcère duodénal, de dyspepsie sans ulcère et de cancer de l'estomac.
Sources de données : Recherche, dans MEDLINE, d'articles publiés en anglais entre janvier 1983 et décembre 1992 à l'aide les termes MeSH *Helicobacter pylori* (appelé *Campylobacter pylori* avant 1990) et ulcère duodénal, cancer de l'estomac, dyspepsie et essai clinique. On a effectué une recherche manuelle dans six journaux et dans *Current Contents* pour y trouver des articles pertinents publiés au cours de la même période.
Sélection d'études : Dans le cas de l'ulcère duodénal, la recherche a été limitée aux études portant sur des adultes, aux études d'éradication du *H. pylori* et aux essais cliniques randomisés comparant un traitement anti-*H. pylori* au traitement conventionnel des ulcères. Dans le cas de la dyspepsie sans ulcère accompagnée d'une infection à *H. pylori*, la recherche a été limitée à des essais cliniques randomisés contrôlés par placebo.
Extraction de données : Chaque auteur a coté la qualité de chaque étude indépendamment, sur une échelle de quatre points. Dans le cas des études sur l'ulcère duodénal, les mesures des résultats évaluées ont été la guérison de l'ulcère aigu et le temps nécessaire à la guérison, l'éradication du *H. pylori* et la réapparition d'ulcères. Dans le cas des études sur la dyspepsie sans ulcère accompagnée d'infection à *H. pylori*, les auteurs ont évalué l'éradication du *H. pylori*, les symptômes utilisés comme mesures des résultats, et déterminé si l'on a utilisé des mesures des résultats validées.
Synthèse des données : Huit essais portant sur l'ulcère duodénal ont satisfait à nos critères d'inclusion : cinq ont été jugés de grande qualité, deux, de qualité raisonnable et un, de faible qualité. Six essais portant sur la dyspepsie sans ulcère ont satisfait aux critères, mais tous ont été jugés faibles. Parmi les traitements possibles, le traitement triple constitué d'un composé de bismuth, de métronidazole et d'amoxicilline ou de tétracycline a permis d'atteindre les taux d'éradication les plus élevés (73 % à 94 %). Les résultats relatifs aux traitements recommandés dans le cas de l'ulcère duodénal ont été uniformes dans toutes les études : lorsqu'on a jumelé un traitement anti-*H. pylori* au traitement conventionnel des ulcères, les ulcères aigus ont guéri plus rapidement. Les taux de réapparition des ulcères ont diminué remarquablement après l'éradication du *H. pylori*. Toutes les études portant sur la dyspepsie sans ulcère ont évalué la clairance (élimination) plutôt que l'éradication du *H. pylori*. Aucune étude n'a utilisé de mesures de résultats validées. L'atténuation régulière de la gravité des symptômes n'a pas été plus importante chez les patients où la bactérie avait été éliminée que chez ceux qui avaient pris un placebo. Aucune des études portant sur le cancer de l'estomac n'a mesuré l'effet de l'éradication du *H. pylori* sur le risque ultérieur de cancer de l'estomac.
Conclusions : Il y a suffisamment de preuves pour appuyer l'administration d'un traitement anti-*H. pylori* chez les patients atteints d'ulcères duodénaux et d'infection au *H. pylori* : le traitement triple donne les meilleurs résultats. Il n'y a pas de preuves à l'appui d'un tel traitement de la dyspepsie sans ulcère chez les patients infectés au *H. pylori*. Il faut accorder beaucoup plus d'attention à la conception des études sur la dyspepsie sans ulcère. Il faut aussi procéder à des études pour déterminer si l'éradication du *H. pylori* chez les patients atteints de gastrite préviendra le cancer de l'estomac.

In the previous article (see pages 177 to 185 of this issue) we critically appraised the evidence for a causal relation between *Helicobacter pylori* infection and gastritis, duodenal ulcer, gastric cancer and nonulcer dyspepsia. In this systematic overview we examine existing treatment options for the eradication of *H. pylori* and evaluate three indications for the treatment of this infection: duodenal ulcer, nonulcer dyspepsia and gastric cancer.

Methods

Relevant articles published from January 1983 to December 1992 were identified through a MEDLINE search with the following MeSH terms: *Helicobacter pylori* (called *Campylobacter pylori* before 1990), gastritis, duodenal ulcer, gastric cancer, dyspepsia and clinical trial. The search included only articles in English. *New England Journal of Medicine*, *Lancet*, *Gastroenterology*, *Gut*, *Digestive Diseases and Sciences*, *American Journal of Gastroenterology* and *Current Contents* were manually searched for other pertinent articles published in the same time frame. We narrowed the search to original trials in which at least 25 patients were enrolled, case reports and reviews. Our search identified 350 articles concerning *H. pylori* and gastritis, 122 concerning duodenal ulcer, 44 concerning gastric cancer and 96 concerning dyspepsia.

These articles, initially located for our evaluation of studies of causation, were analysed further to evaluate efficacy of treatment. The analysis focused on successful eradication of *H. pylori* rather than suppression or clearance of the organism. We agree with the methods and conclusions of a recently published thorough meta-

analysis of the efficacy of antibiotic therapy in eradicating *H. pylori*.[1] Therefore, instead of repeating a meta-analysis of treatment efficacy we summarized the advantages and disadvantages of currently available treatment options.

For duodenal ulcer the search was narrowed to studies involving adults (over 17 years of age), randomized clinical trials in which anti-*H. pylori* therapy was compared with conventional ulcer treatment and studies that used eradication of *H. pylori* as an outcome measure. Open label studies, case series and studies published as letters to the editor or as abstracts were excluded.

For patients with nonulcer dyspepsia and *H. pylori* infection the search was limited to placebo-controlled randomized clinical trials involving adults. In this case outcome measures were clearance or eradication of *H. pylori*. Clearance of *H. pylori* was included because temporary suppression of the organism can also lead to a decrease in symptom severity.

For gastric cancer all studies of the link between gastric cancer and *H. pylori* were evaluated. However, none of these studies examined the effect of eradication of *H. pylori* on the subsequent risk of gastric cancer.

We assessed the following outcome measures. Duodenal ulcer: acute ulcer healing and time required for healing, eradication of *H. pylori* and ulcer relapse; nonulcer dyspepsia in patients with *H. pylori* infection: eradication of *H. pylori*, the symptoms used as outcome measures and whether validated outcome measures were used.

The studies were assessed independently by each of us for their quality on a four-point scale: +++ for a high-quality study (methodologically strong without important weaknesses), ++ for one of reasonable quality (some weaknesses in study design or results), + for a weak study (definite shortcomings in design or results) and 0 for a poor study (serious weaknesses).

Primary outcome measures of all the articles were also independently assessed by each of us. We reached a consensus on quality scores of the articles and on data presentation through discussion. Since the studies included in the analysis varied in treatment protocols used, duration of treatment, timing of study endpoints and length of follow-up, we did not pool data for statistical analysis.

Results

Determination of eradication

There is consensus that it is important to distinguish suppression (or clearing) of the organism from eradication.[2] It is now accepted that investigations cannot be repeated until at least 4 weeks after a course of treatment has been completed to determine whether *H. pylori* is still present.[3,4] If one investigates earlier it may be difficult to identify and culture the organism even though bacterial colonization is only temporarily suppressed. Recrudescence invariably occurs if the bacteria have not been eradicated.[3,4] Five types of diagnostic tests are currently available: histologic testing, culture, rapid urease testing, ^{13}C or ^{14}C urea breath testing and serologic testing (e.g., enzyme-linked immunosorbent assay). All diagnostic tests perform well, with sensitivities of more than 80% and specificities of more than 95%.[5] The current gold standard for detecting *H. pylori* is a combination of culture,[6] histologic test (with hematoxylin–eosin stain, modified Giemsa stain, or Steiner or Warthin–Starry silver stain) and, if available, rapid urease test. Although the antrum is the most commonly affected portion of the stomach, the presence of *H. pylori* may be patchy on the gastric mucosa and can be missed if only a single biopsy specimen is taken. The most commonly used method to determine eradication is to take four gastric biopsy specimens — two from the antrum and two from the body — during a follow-up endoscopy for culture and histologic testing. With the use of this protocol the presence of *H. pylori* will be correctly assessed in more than 90% of patients.[4,5]

Existing treatment options

H. pylori has proven difficult to eradicate. Unfortunately, the organism's susceptibility to a treatment in vitro is a poor predictor of clinical efficacy.[7,8] Antacids, H_2-receptor antagonists, sucralfate and misoprostol have no effect.[9] The role of omeprazole is still unclear.[10–12] It suppresses growth of the organism in vitro but probably does not eradicate it in vivo when used alone.[13,14]

The highest eradication rates of monotherapy are achieved with a bismuth compound (20%) and amoxicillin (23%).[1] Most dual therapies, such as bismuth–amoxicillin, bismuth–metronidazole and amoxicillin–metronidazole, achieve eradication in less than 55% of cases.[1]

The best treatment results are achieved with combinations of three drugs (triple therapy). The most successful combination is a bismuth compound, metronidazole (usually 500 mg three times a day) and either amoxicillin (500 mg three times a day) or tetracycline (500 mg four times a day). In North America bismuth subsalicylate is the only bismuth preparation available. In contrast, most European and Australian centres use bismuth subcitrate. The distinction between the two compounds may be important because they may differ in their bioavailability and in their mechanisms of action.[15,16] The commonly used dosage of bismuth subsalicylate is two tablets four times a day. The duration of treatment is generally 2 weeks, but 1 week may be equally effective.[17] Compliance with therapy is an important predictor of success.[18]

A recent meta-analysis of treatment efficacy concluded that the triple therapy combination of bismuth,

metronidazole and tetracycline is superior to bismuth, metronidazole and amoxicillin (eradication rate 94% v. 73%).[1] A disadvantage of the triple therapy with tetracycline is that it should not be used in young children and pregnant women. In addition, as discussed by the authors of the meta-analysis, the designs of many of the studies included in their analysis were suboptimal.[1] Furthermore, the duration and dosages of medications varied considerably. Most important, these results do not take into account metronidazole resistance in *H. pylori*,[19] which is an important predictor of treatment failure. For example, one study showed that triple therapy with amoxicillin achieves eradication of metronidazole-sensitive strains in 93% of patients, but if *H. pylori* strains are resistant to metronidazole before treatment the eradication rate decreases to only 24%.[17] There are wide geographic variations in the prevalence of metronidazole-resistant strains: 20% to 80% in Western Europe, almost 100% in Africa[20,21] and 30% in Nova Scotia.[22] The reasons for this variation are unclear, although in Africa frequent over-the-counter use of metronidazole for intercurrent illnesses is one explanation for the organism's resistance to

Table 1: Randomized controlled trials of treatment of *Helicobacter pylori* (Hp) infection in patients with duodenal ulcer

Study (and quality score*)	Treatment group†	Outcome; no. (and %) of patients			Comments
		Ulcer healed	Hp eradicated	Relapse‡	
Marshall et al[28] (++)	Cim 400 mg bid × 8 wk, placebo resembling Tin (n = 22)	(at wk 10) 13/22 (59)	0/22	(at 1 yr) 12/22 (55)	
	Cim 400 mg bid × 8 wk, Tin 500 mg bid × 10 d (n = 29)	22/29 (76)	1/29 (3)	18/29 (62)	
	CBS 480 mg qid × 8 wk, placebo resembling Tin (n = 22)	15/22 (68)	5/22 (23)	8/22 (36)	
	CBS 480 mg qid × 8 wk, Tin 500 mg × 10 d (n = 27)	20/27 (74)	19/27 (70)	5/27 (19)	
(Treatment groups combined according to Hp status)	Hp negative at wk 10 (n = 25)	23/25 (92)	25/25 (100)	5/25 (20)	
	Hp positive at wk 10 (n = 75)	47/75 (63)	0/75	38/75 (51)	
Rauws et al[29] (++)	CBS 1 tab qid d 1–28 plus Amo 375 mg tid d 1–28 plus Met 500 mg tid d 18–28; Ran 150 mg od d 29–56 (n = 24)	(at wk 8) 17/19 (89)	15/19 (79)	(at 1 yr) 1/17 (6)	5 pts withdrew because of side effects. The 1 pt who had a relapse was Hp positive at wk 8
	CBS 1 tab qid × 28 d, Ran 150 mg d 29–56 (n = 26)	21/26 (81)	2/26 (8)	16/21 (76)	No relapse occurred in the 2 pts who were Hp negative at wk 8
Graham et al[30] (+++)	Ran 300 mg × 16 wk; BSS 151–302 mg d 1–14 plus Tet 500 mg qid d 1–14 plus Met 250 mg tid d 1–14 (n = 53)	(at wk 4) 39/53 (74) (at wk 8) 44/53 (83) (at wk 16) 52/53 (98)	43/45 (96)	NM	2 pts were Hp negative before treatment. In 43 pts Hp was eradicated, in 2 pts eradication failed, and in 6 Hp status was unknown

*See Methods section for system of scoring quality.
†Cim = cimetidine, Tin = tinidazole, CBS = colloidal bismuth subcitrate, Amo = amoxicillin, Met = metronidazole, Ran = ranitidine, BSS = bismuth subsalicylate, Ome = omeprazole, Tet = tetracycline.
‡NM = not measured.

it.[23] The precise mechanism of metronidazole resistance in *H. pylori* is unclear and requires detailed investigation. The addition of a bismuth compound to the antibiotic therapy for *H. pylori* infection offers some protection against metronidazole resistance.[24–26]

Most recently, the combination of high-dose omeprazole (40 mg twice daily) and amoxicillin (1 g twice daily) has yielded eradication rates as high as 82%.[27,28] Further evaluation is needed to determine whether these higher rates are caused by improved efficacy of amoxicillin resulting from increased acid suppression or by an anti-*H. pylori* effect of omeprazole.

Specific indications for treatment

We agreed fully on the quality scores of the eight duodenal ulcer studies and the six nonulcer dyspepsia trials.

Duodenal ulcer: Of the 122 identified clinical trials of the relation between *H. pylori* and duodenal ulcer, 8 fulfilled our entry criteria of adult participants, random

Study (and quality score*)	Treatment group†	Outcome; no. (and %) of patients			Comments
		Ulcer healed	Hp eradicated	Relapse‡	
Graham et al[30] (+++)	Ran 300 mg × 16 wk (n = 52)	(at wk 4) 27/52 (52) (at wk 8) 32/52 (62) (at wk 16) 44/52 (85)	0/52	NM	
Hosking et al[31] (+++)	Ome 40 mg × 4 wk, CBS 120 mg qid d 1–7 plus Tet 500 mg qid d 1–7 plus Met 400 mg qid d 1–7 (n = 78)	(at wk 8) 70/74 (95)	70/74 (95)	NM	4 pts lost to follow-up
	Ome 40 mg × 4 wk (n = 77)	56/72 (78)	3/72 (4)	NM	5 pts lost to follow-up
Bayerdorffer et al[32] (+++)	Amo 1 g bid d 1–10, Ome 40 mg bid d 1–10, Ome 20 mg d 11–26 (n = 30)	(at wk 6) 27/27 (100)	22/27 (82)	(at 9 mo) 0/27	3 pts lost to follow-up
	Ome 40 mg bid d 1–10, Ome 20 mg d 11–26 (n = 30)	25/26 (96)	0/26	12/25 (48)	5 pts lost to follow-up
Hentshel et al[33] (+++)	Amo 750 mg tid d 1–12, Met 500 mg tid d 1–12, Ran 300 mg × 6 wk (n = 52)	(at wk 6) 48/52 (92)	46/52 (88)	(at 1 yr) 4/46 (9)	6 pts lost to follow-up. Only 1 of 46 pts who were Hp negative at wk 6 had a relapse. 8 pts taking antibiotics had side effects, as compared with 1 in Ran group
	Ran 300 mg × 6 wk (n = 52)	39/52 (75)	1/52 (2)	42/45 (93)	7 pts lost to follow-up

allocation and *H. pylori* eradication as an outcome measure.[28–35] Five studies were high quality, two were of reasonable quality, and one was weak. Table 1 summarizes the studies that investigated the effect of anti-*H. pylori* treatment on healing of the acute ulcer or on relapse or both, and Table 2 shows the studies that examined relapse and *H. pylori* status after the initial ulcer had healed. For clarification of the data in the study by Marshall and associates[28] Table 1 shows the results according to the four treatment arms and *H. pylori* status after treatment.

As shown in these tables, the treatment regimens, duration of treatment, frequency of repeat endoscopies and length of follow-up varied considerably among the studies. Although the data were not pooled for statistical analysis the results of each of the studies were highly consistent. In the most recent studies investigators used triple therapy, whereas Marshall and associates[28] used dual therapy and Coghlan and collaborators[34] used monotherapy. These earlier studies showed higher relapse rates likely because monotherapy and dual therapy are not nearly as effective as triple therapy in eradicating *H. pylori*. With adequate compliance triple therapy results in ulcer relapse rates of less than 10% at 1-year follow-up. Thus, if *H. pylori* is eradicated, the natural history of duodenal ulcer disease is altered dramatically. The results also clearly demonstrate that anti-*H. pylori* treatment in addition to conventional duodenal ulcer treatment increases the speed of healing of the acute ulcer.[30]

Although up to 45% of patients experience side effects from dual or triple therapy[18] these are usually minor and consist of nausea, loose stools, dizziness and heartburn. For most patients these side effects are not serious enough to discontinue the medication.

Nonulcer dyspepsia: Of the 96 clinical studies that examined the relation between dyspepsia and *H. pylori* infection 6 fulfilled our entry criteria of adult participants, use of a placebo group and random allocation.[36–41] The quality of all the studies was rated as weak due to poor description of symptom measurement and measurement scales, lack of use of validated outcome measures and short duration of follow-up. The results of the studies and their quality scores are summarized in Table 3.

These studies varied markedly concerning duration of treatment, which symptoms were considered outcome measures, how severity of symptoms was assessed and how a decrease in symptom severity was measured. None of the studies used a previously validated outcome measure, and we have reservations about the methods used for symptom measurement in most of these studies. All of the studies examined clearance of *H. pylori* instead of eradication. The follow-up period was short, varying between 4 and 8 weeks. Only one of the six studies showed a greater decrease in symptom severity in the treatment group than in the placebo group. On the basis of these results, there is no evidence to support anti-*H. pylori* treatment in patients with nonulcer dyspepsia who have *H. pylori* infection.

Gastric cancer: Of the 44 articles examining the association between *H. pylori* and gastric cancer none investigated the effect of eradication of *H. pylori* on the subsequent risk of gastric cancer. Therefore, anti-*H. pylori* treatment for this indication cannot be recommended at this time.

Table 2: Randomized controlled trials of duodenal ulcer relapse and Hp status in patients whose acute ulcer had healed

Study (and quality score)	Treatment group	Outcome; no. (and %) of patients		Comments
		Hp eradicated	Relapse	
Coghlan et al[34] (+)	CBS 120 mg qid × 6 wk (n = 23)	12/23 (52)	(at 1 yr) 11/21 (52)	2 pts lost to follow-up
	Cim 400 mg bid × 6 wk (n = 23)	4/23 (17)	12/18 (67)	5 pts lost to follow-up
Graham et al[35] (+++)	Ran 300 mg × 16 wk; BSS 151–302 mg d 1–14 plus Tet 500 mg qid d 1–14 plus Met 250 mg tid d 1–14 (n = 47)	40/47 (85)	(at 9 mo) Hp negative 3/40 (8) Hp positive 4/7 (57)	
	Ran 300 mg × 16 wk (n = 36)	0/36	34/36 (94)	

Discussion

Given the several strategies we used to identify studies for our review, it is unlikely that we missed any eligible studies. More important, even if we had, the omission would likely not have altered our conclusions. However, the literature on *H. pylori* is rapidly expanding.[42] Many recent studies of the efficacy of new treatment combinations to eradicate *H. pylori* are available only in abstract form or suffer from poor study design or both[1] and thus were not included in this analysis.

We feel that there is compelling evidence to recommend anti-*H. pylori* treatment of relapsing duodenal ulcers. Eradication of *H. pylori* leads to a dramatic reduction in ulcer relapse rates, from between 60% and 80% 1 year after treatment to less than 10%.

Because anti-*H. pylori* therapy not only speeds healing of the acute ulcer but also, with conventional acid suppressive therapy, achieves higher healing rates, it can be considered when the ulcer is first diagnosed.[43] However, since as many as 20% to 40% of ulcers in patients with *H. pylori* infection do not recur, anti-*H. pylori* therapy may be delayed until the first ulcer relapse, particularly if the patient has other risk factors for ulcer recurrence, such as smoking. This approach is in agreement with the cautious recommendations of the working party on *H. pylori* presented at the 1990 World Congress of Gastroenterology.[44] Although no study has yet formally examined subgroups of patients with duodenal ulcer, we recommend anti-*H. pylori* therapy in patients with peptic ulcer complicated by bleeding or perforation or those for whom anti-ulcer surgery is contemplated.

These recommendations concern only duodenal ulcers that are not caused by nonsteroidal anti-inflammatory drugs (NSAIDs). It is possible that ulcerogenic medications such as NSAIDs exacerbate a predisposition to ulcers in patients with *H. pylori* infection. However, there are no data to support this hypothesis. The prevalence of *H. pylori* is not affected by the use of NSAIDs.[45,46]

All recent studies of treatment examined dual or triple therapy (to which acid suppressive therapy is sometimes added). Side effects are experienced by up to 45% of patients undergoing therapy,[18] but they are usually mild and rarely cause discontinuation of treatment. With the existing treatment combinations cost is not a major issue, although newly launched antibiotics will probably be expensive. However, successful eradication of *H. pylori* is cost-effective since expensive maintenance therapy is no longer required.

In addition, nonrandomized studies of anti-*H. pylori* treatment in patients with duodenal ulcer have shown much lower recurrence rates than expected given the tendency of duodenal ulcers to relapse.[47–49] In all studies low ulcer recurrence rates coincide with low *H. pylori* reinfection rates (less than 10%) 1 year after treatment.[31,32,47,50]

It is not known which people with *H. pylori* infection will have duodenal ulcers. The prevalence of *H. pylori* in the general population is high.[51,52] In a study involving randomly selected people in Nova Scotia the prevalence of *H. pylori* infection varied from 21% among people 18 years of age to 50% among those over 70.[53] Most people infected with *H. pylori* are asymptomatic[54–57] and will never have peptic ulcers.

Table 3: Randomized placebo-controlled trials of treatment to clear* existing Hp infection in patients with nonulcer dyspepsia

Study (and quality score)	Treatment†	Length of follow-up	Primary outcome measures‡	Study conclusions	Comments
Morgan et al[36] (+)	Nit × 2 wk, Fur × 2 wk (n = 106)	6 wk	Seven symptoms and length of time to disappearance of symptoms	No change in symptoms	Poor definition of symptoms
Glupczynski et al[37] (+)	Amo × 8 d (n = 45)	7 wk	Summation of severity of six symptoms	No difference	Poor definition of symptoms
Lambert et al[38] (+)	CBS × 4 wk (n = 50)	5 wk	Summation of severity of six symptoms	Some improvement if Hp cleared	Importance of some symptoms questionable
Loffeld et al[39] (+)	CBS × 4 wk (n = 50)	5 wk	Five symptoms and change in global assessment	No difference	Unclear measures of severity and global assessment
Kang et al[40] (+)	CBS × 8 wk (n = 51)	8 wk	Global assessment	No difference	Unclear measure of global assessment
Goh et al[41] (+)	CBS × 4 wks (n = 40)	4–8 wk	Five symptoms and global assessment	Symptom severity decreased if Hp cleared	Unclear measure of change in symptom severity

*See the Results section for discussion of clearance.
†Nit = nitrofurantoin, Fur = furazolidone.
‡None of the studies selected used validated outcome measures of symptoms; see also the Results section, Specific indications for treatment.

Although we did not review the subject in this analysis, *H. pylori* infection may also play an important role in gastric ulcer formation. Approximately 70% of gastric ulcers occur in patients who have *H. pylori* infection.[58] For gastric ulcers insufficient data are available to recommend specific therapeutic intervention against *H. pylori*. However, one study demonstrated a decrease in the rate of gastric ulcer relapse from 74% to 13% after eradication of *H. pylori*.[35]

Gastric ulcer is associated with multifocal atrophic gastritis, unlike duodenal ulcers, which are accompanied by a diffuse nonatrophic (type B) antral gastritis.[59] The reason some people have antral-predominant gastritis and others multifocal atrophic gastritis is unknown, although a high level of acid secretion has been suggested as a predisposing factor for diffuse antral gastritis.[60] Atrophic gastritis is linked to the subsequent development of gastric cancer. There is no current evidence that treatment of *H. pylori*-associated gastritis will prevent gastric cancer. Therefore, the presence of *H. pylori* gastritis in the absence of peptic ulcers is not an indication for antibacterial treatment.

Gastric cancer is still an important cause of death worldwide. However, in the United States and Canada the incidence and associated mortality rates of gastric cancer have declined steadily over many decades.[61] One explanation for this observation is that people in developed countries acquire *H. pylori* at a higher age than people elsewhere, and the duration of gastritis may determine the subsequent risk of gastric cancer.[62] If this hypothesis is proven, then prevention or treatment of *H. pylori* infection in young people may be a way to prevent gastric cancer. However, this prevention technique would apply only to populations in which the prevalence of both *H. pylori* infection and gastric cancer is high.

Children and adults with type B gastritis and nonulcer dyspepsia who have *H. pylori* infection are the largest group of patients with gastrointestinal symptoms seen in clinical practice. About 40% to 60% of adult patients with nonulcer dyspepsia have *H. pylori* infection.[5,57,63,64] To date, no underlying pathophysiologic mechanism has unequivocally explained functional dyspepsia.[65,66] All definitions of functional dyspepsia include its cardinal symptoms — chronic (persistent or intermittent for at least 3 months) or recurrent (present at least 25% of the time) discomfort or pain in the upper part of the abdomen that often affects a patient's ability to concentrate on daily activities.[67,68] Unfortunately, much more attention has been paid to the criteria for diagnosing functional dyspepsia than to the methods for evaluating its severity. Knowledge about the effect of treatment on symptoms and their severity is crucial in making a rational decision to treat patients with nonulcer dyspepsia.[69]

Many nonulcer dyspepsia trials suffer from methodologic problems, especially the lack of validated methods for measuring symptoms and their severity as outcome variables.[66,70,71] The studies reviewed in this analysis suffer from these problems as well as a short follow-up period and examination of clearance of the organism instead of eradication. The last shortcoming may be due to the fact that triple therapy was not yet firmly established when these studies were begun. Of course, the subgroup of patients with nonulcer dyspepsia and *H. pylori* infection may find that their symptoms are significantly alleviated after eradication of the organism. However, such an effect must and can only be demonstrated in a double-blind placebo-controlled trial. On the basis of our systematic overview treatment of these patients cannot be recommended at this time. Furthermore, gastritis in the absence of peptic ulcers is not sufficient grounds to warrant anti-*H. pylori* therapy.

Triple therapy offers the best chance of *H. pylori* eradication, although additional long-term data on the efficacy of anti-*H. pylori* treatment regimens are still required. Better treatments will likely become available. Compliance with therapy is important. The eradication rate is 96% in patients who take more than 60% of their medication, but drops to 69% in those who take less than 60% of their medication.[18] Nausea and diarrhea are the most common side effects with triple therapy regimens, and up to 45% of patients experience these side effects.[1,18,30,31] Colitis caused by *Clostridium difficile* has occasionally been reported.[72,73]

Conclusions

We recommend anti-*H. pylori* therapy be prescribed for all patients with relapsing duodenal ulcers who have *H. pylori* infection. Such treatment could also be considered at the first presentation of duodenal ulcer with *H. pylori* infection, since the relapse rate after standard antiulcer therapy is so high. Acid suppressive therapy added to triple therapy will increase the speed of healing and result in a higher ulcer healing rate. Currently, there is no evidence to support anti-*H. pylori* therapy in patients with *H. pylori* infection who do not have duodenal ulcers. The methods used in all published trials of treatment in patients with *H. pylori* infection and nonulcer dyspepsia are poor. Much more attention needs to be paid to the design of such studies. Whether *H. pylori*-associated gastritis should be treated to prevent gastric cancer should be studied. Changes in treatment recommendations need to be based on additional data from randomized controlled clinical trials.

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