Helicobacter Pylori - Its Role and Treatment in Gastrointestinal Diseases

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ABSTRACT

With gastrointestinal illnesses affecting a large percentage of the population, it is not surprising that ***Helicobacter pylori*** *has received much recent attention. The purpose of this article is to discuss the role of* H. pylori *in these illnesses as well as the various drug regimens used to eradicate it. While* H. pylori *has been found to cause type B gastritis, such a relationship has been more difficult to establish for peptic ulcer disease (PUD). It is known; however, that eradication of* H. pylori *leads to similar ulcer healing rates as those achieved with* H_2*-receptor antagonists or omeprazole, but causes a significant decrease in ulcer relapse rates compared with conventional therapies. The population in which* H. pylori *treatment may be indicated has recently been extended to include all patients with* H. pylori *infection and peptic ulcer disease, whether initial or recurrent. Triple therapy containing bismuth and two antimicrobial agents has been the main treatment regime directed against* H. pylori. *However, this is changing as omeprazole-antibiotic combinations show promising results.*

Key Words: *bismuth, gastrointestinal illnesses, Helicobacter pylori, omeprazole, peptic ulcer disease, triple therapy*

RÉSUMÉ

Les affections gastro-intestinales touchent un fort pourcentage de la population. Aussi, n'est-il pas surprenant de voir que Helicobacter pylori ait retenu tant l'attention dernièrement. L'objet de cet article est d'examiner le rôle de H. pylori dans ces affections ainsi que les divers régimes thérapeutiques utilisés pour éradiquer ce microorganisme. Bien qu'on sache que H. pylori cause la gastrite de type B, il a été plus difficile d'établir ce lien de causalité dans le cas des ulcères gastro-duodénaux. On sait cependant que l'éradication de H. pylori entraîne un taux de cicatrisation des ulcères semblable à celui qu'on obtient avec les antagonistes des récepteurs H_2 *ou l'oméprazole, mais qu'elle cause une diminution marquée des taux de récidives des ulcères comparativement avec les traitements classiques. On a récemment étendu l'indication du traitement de H. pylori à tous les patients présentant une infection à H. pylori ou un ulcère gastro-duodénal initial ou récidivant. Le traitement d'association triple avec bismuth et deux agents antimicrobiens constitue la principale modalité thérapeutique d'éradication de H. pylori. Cela pourrait cependant bien changer, puisque les associations oméprazole-antibiotique montrent des résultats prometteurs.*

Mots Clés: affections gastro-intestinales, bismuth, *Helicobacter pylori*, oméprazole, traitement d'association triple, ulcère gastro-duodénal

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INTRODUCTION

Gastrointestinal illnesses (GI), and in particular peptic ulcer disease (PUD), cause much morbidity in most segments of the population. Much attention has been given to the treatment of this universal health problem, and the recent insight into the contribution of *Helicobacter pylori* has given a different perspective to treatment approaches.

H. pylori, a Gram-negative organism, was first reported as being an important factor in PUD by Marshall and Warren in 1982.[1] Since then much attention has been given to this microbe with more than 2,500 papers written on it.[2] It is now known that eradication of *H. pylori* infection cures type B gastritis and dramatically changes the course of idopathic PUD with a significant decrease in ulcer relapse rates.[3-9] Despite there being much insight into this area, a causal relationship between PUD and *H. pylori* and a mechanism to describe the association between the two has been difficult to establish. And although some treatments have provided good results, an ideal drug regimen for eradication of *H. pylori* is yet to be discovered.

The purpose of this article is to evaluate the role *H. pylori* plays in gastrointestinal illnesses and the treatments used to eradicate it.

ROLE IN DISEASE

A true causal relationship between *H. pylori* and gastrointestinal disease has only been established for

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gastritis. However, a strong association between it and other GI illnesses has been found. In one study, it was noted that the organism was detected in the gastric antral mucosa in 74% of patients with peptic disease.[10] Rauws et al discovered that 98% of ulcer patients and 70% of non-ulcer dyspepsia patients were *H. pylori* positive, while the organism was present in only 20-30% of asymptomatic volunteers.[3,11,12]

Gastritis

Gastritis is subdivided into type A and type B. These have different etiologies and only the latter is associated with the colonization of *H. pylori*.

It has by now been well established that *Helicobacter pylori* causes chronic active type-B gastritis with the following evidence. This type of gastritis is present in virtually all *H. pylori* positive patients, is resolved once the infection is eliminated, is reproduced following the ingestion of the organism, is reproducible with recolonisation of *H. pylori* and is more prevalent in the elderly who also have a higher incidence of the infection.[3,5,13,14,15] In another study, Dehesea et al found that the overall occurrence of *H. pylori* infection was much higher in Hispanic patients, being present in 79% of all asymptomatic cases, and all but one out of 58 patients also presented with gastritis.[16] Gastritis is also significantly more prevalent in developing countries where *H. pylori* infections occur much sooner in life.[17]

Whereas a casual relationship between *H. pylori* and type-B gastritis exists, type-A gastritis is believed to be associated with achlorhydria and an autoimmune abnormality seen in patients with pernicious anaemia.[18,19] In this type of gastritis as well as the kind caused by non-steroidal anti-inflammatory drugs (NSAIDs) there is usually no *H. pylori* infection, indicating that the organism does not merely colonize damaged mucosa.[19]

Peptic Ulcer Disease

Although not all of Koch's postulates for linking the organism to the disease have been fulfilled due to the lack of an animal model, the role of *H. pylori* as a pathogenic factor in ulcer disease is now well established.[17,20] Only a fraction of all patients with *H. pylori* infections develop PUD, yet 98% of patients with duodenal ulcers and 80-93% of patients with gastric ulcers not due to drugs are *H. pylori* positive.[21,22] To further support the association between organism and disease, it has been shown that eradication of the organism with antibiotics leads to similar ulcer healing rates as those achieved with H_2-receptor antagonists or omeprazole.[23,24] Additionally, eradication of *H. pylori* has caused a significant decrease in ulcer relapse rates.[5,6,25,26] In one study, relapse occurred in 12% of patients with duodenal ulcers and in 13% of patients with gastric ulcers, who were treated with triple therapy to eradicate *H. pylori* plus ranitidine.[8] In comparison, of those patients receiving the H_2-receptor antagonist alone, 95% with duodenal and 74% with gastric ulcers experienced ulcer relapse within the two-year follow-up period.

Whether or not the rate of healing improves with the treatment of *H. pylori* infection as described in some studies, remains questionable.[27,28]

Some evidence against a causal association between *H. pylori* infection and PUD include the following:[5,17,23,20] 1) duodenal ulcers occur more frequently in males, whereas *H. pylori* infections are independent of gender; 2) *H. pylori* is more prevalent with increasing age, but duodenal ulcers are not; 3) ulcers heal even without eradication of the organism; and 4) many people with the infection never develop ulcers.

Therefore, although one can assume that *H. pylori* plays a critical role in the pathogenesis of peptic ulcer disease, other factors may also be required. In some cases these may include cigarette smoking, the use of NSAIDs, stress, heredity, and hypersecretion of gastric acid as in Zollinger-Ellison Syndrome, the latter in which ulcers occur in the absence of *H. pylori*.[4,12,19,20]

Other GI Illnesses

The role of *H. pylori* in non-ulcer dyspepsia remains unclear since a direct association has not yet been detected.[18,19] Nicholas et al described a possible mechanism where infection itself, as well as chronic gastritis caused by it, decrease grastic motility, which in turn may produce chronic dyspepsia by damaging afferent nerves.[26,29]

An association between *H. pylori* and gastric cancer can possibly be the most important finding.[16,30-33] It should be emphasized that it is too early to conclude from these studies that eradication of the organism will significantly decrease the incidence of gastric malignancy; however, findings of a possible relationship between the two signify the importance for further investigation in this area. In three independent studies, it was found that *H. pylori* infection increases the risk of developing gastric cancer four- to six-fold.[30-33] Epidemiologic studies have also shown a positive correlation.[5,16,19]

Lastly, it has been reported by Mocek et al that elimination of *H. pylori* causes a disappearance of hyperplastic gastric polyps.[34]

DIAGNOSIS

H. pylori can be detected either by invasive or non-invasive methods. Invasive methods include culture and histologic staining of biopsy specimens and are traditionally considered the gold standard, yet they are the least sensitive diagnostic test (70-80%).[5,20] The detection of urease activity is another invasive method and has been determined to have sensitivities and specificities >90%.[5,21] The non-invasive tests have excellent diagnostic sensitivities and specificities (>95%) for the initial diagnosis.[5] Among these are the urea breath test and serology tests for IgG antibodies

to *H. pylori*. Although further studies are required to determine the reliability of serology tests, the urea breath test has been shown to be both sensitive (90-100%) and specific (95-100%).[5,21] More recently, saliva has been tested for *H. pylori* IgG and IgA with a sensitivity and specificity of 82% and 71%, respectively. However, to date, it is not preferred over serological testing.[35] Serological testing is now available at some provincial laboratories.

TREATMENT

The treatment for *H. pylori* poses several unique challenges. The organism colonizes under a mucus layer in a protected and highly acidic environment, which alone causes a significant decrease in the antimicrobial activity of most drugs.[5] Further, resistance due to either the inoculum effect or the emergence of *H. pylori* subpopulations may be present.[20] Again, the lack of an animal model adds further difficulty in the study for an ideal treatment regimen.[5] Lambert defined the ideal properties of a drug against *H. pylori* as having rapid dissolution and good dispersion in the stomach, stability and activity at a low pH, size and charge suitable for mucus penetration, absorption or secretion via gastric mucosa, good activity against *H. pylori*, low susceptibility to acquired resistance and minimal local and systemic effects.[36] These are difficult to achieve with a single agent, accounting for the fact that all studies have shown a superiority of combination therapy, with monotherapy being mostly unsuccessful as a method of eradication.[3,6,19,37] Multiple drugs administered at various times of the day can greatly affect patient compliance and incidence of side effects, however.[5] Thus, the discovery of a simple and safe two- or three-drug regimen is of great importance. Since development of resistance to and recurrence (rather than reinfection) of *H. pylori* due to incomplete eradication of the organism pose further problems, many investigators recommend that antimicrobial treatment last for two weeks. There have also been questions regarding the need for maintenance antisecretory therapy following the eradication of *H. pylori*. This has been recommended if the PUD is active.[5] However, according to a study by Sung et al, a low relapse rate of gastric ulcers (4.5%) in patients treated solely with triple therapy suggests that additional antisecretory therapy may not be necessary.[24]

Treatment can be termed successful if the organism is eradicated, which in turn is defined as negative cultures four to six weeks after cessation of therapy.[20,38,39] From the studies conducted to date, it can be assumed that successful eradication of *H. pylori* will cure the majority of duodenal ulcers unless reinfection occurs.

Specific treatments which have been studied and used clinically are outlined below.

Triple Therapy

A triple antimicrobial regimen, consisting of a bismuth compound, metronidazole, and tetracycline, is the most extensively studied combination therapy. It yields eradication rates of about 90%, which is reduced to approximately 80% if amoxicillin is substituted for either tetracycline or metronidazole.[5,40] Other combinations with bismuth seem less promising (Table I). These eradication rates may depend on bacterial density; however, as shown by Moskkowitz et al. Using triple therapy (bismuth, metronidazole, and amoxicillin), they achieved an average eradication rate of 64.4%, but once classified according to pretreatment urease activity, these ranged from 37.5 to 87.8% between patient with high to low activity.[43]

These regimens are rather complicated and 21 to 32% of patients suffer side effects.[17,19,27] Both can lead to discontinuation of treatment. Resistance, in particular to metronidazole, poses another potential problem.[5,17] Should this develop or the patient be unable to tolerate metronidazole or tetracycline, amoxicillin can be substituted for either one with little loss in efficacy.[5,21,40]

As mentioned earlier, it is recommended that antibiotic treatment be continued for two weeks. However, in a study performed by Hosking et al, a one-week course of triple therapy, including bismuth, tetracyline, and metronidazole plus omeprazole for four weeks was just as effective, as assessed by culture and urease testing.[44]

Bismuth compounds, which have been used in the treatment of gastro-intestinal disorders for decades, poses activity against *H. pylori* with an eradication rate of about 20% when used alone.[12,45] Although in most cases bismuth monotherapy is not capable of eliminating the organism, it is however able to suppress it.[37] Additionally, this group of compounds is thought to affect the healing of ulcers by stimulating prostaglandin and mucus production and modulating the immune response.[12] The exception is bismuth subsalicylate, which demonstrates a reduction in mucosal PGE_2-generation.[27,46]

Table I: Eradication Rates using Different Regimens Containing Bismuth

DRUG(S)	ERADICATION RATES	REFERENCES
bismuth, metronidazole, tetracycline	90%	5
	94%	40
	87%	41
	~90%	21
bismuth, metronidazole, amoxicillin	>80%	5
	73%	40
bismuth, amoxicillin, tetracycline	>80%	5
	43%	42
bismuth, amoxicillin	40%	3
	44%	40
bismuth, metronidazole	55%	40
bismuth	18%	3
	20%	40

> - greater than, as determined by the NIH Consensus Development Panel [5]
~ - approximately, as determined by the NIH Consensus Development Panel [21]

It was; therefore, concluded that this form of bismuth diminishes the protective mechanism in *H. pylori* positive patients and may not be the preferred preparation. However, bismuth subsalicylate is the only form available in Canada and, as mentioned above, as part of triple therapy combination, shows good efficacy in eradicating the organism and in assisting directly or indirectly in the healing of PUD.

Common side effects of the bismuth component in triple therapy include blackened stools, mild dizziness and headache, nausea, vomiting, and diarrhea.[47] Since bismuth is stored in body tissues, the use of high doses or treatment for prolonged periods of time may lead to decreased safety.[47]

Metronidazole has only moderate activity against *H. pylori* but it is still an important agent in the regimen for two reasons: it possesses pH independent antimicrobial activity and is secreted in the stomach with a high concentration being attained in the gastric juices.[17]

The combination of metronidazole, amoxicillin, and ranitidine has also been evaluated.[9] It resulted in good efficacy (84% eradication) and somewhat lower incidence of side effects (15%) than the one containing bismuth. Therefore, this treatment may be an alternative although resistance to metronidazole would again need to be taken into consideration.

Dual Therapy

With respect to dual therapy for *H. pylori*, the combination of omeprazole and amoxicillin has received recent attention. Several studies have demonstrated eradication rates greater than 80%.[5] However, there seems to be variability in results for yet an unknown reason.[48] The rationale behind this combination stems from the discoveries that omeprazole has antimicrobial properties enough to diminish but not to eradicate *H. pylori*, and that amoxicillin has good activity against *H. pylori in vitro*.[36,49,50] Due to omeprazole-induced reduction in gastric acid, amoxicillin can retain this activity *in vivo*.[49] This regimen has the advantage of being a simpler and better tolerated treatment compared to bismuth-containing triple therapy.[49,51,52]

Labenz et al conducted two studies to compare different dosages and durations of therapies involving omeprazole and amoxicillin with the following conclusions:[38,49] omeprazole at a dose of 40 mg daily raises the pH for sufficient amoxicillin activity. This is in agreement with Savarino et al.[53] The duration of omeprazole seems to be important with higher efficacy occurring in a two-week compared to one-week treatment. Lastly, omeprazole pretreatment may decrease the bacterial sensitivity to amoxicillin, which was explained by the hypothesis that omeprazole may induce coccoid persister forms of *H. pylori*. This was also concluded by Adamek et al, who studied a three-day course of intravenous omeprazole and amoxicillin before switching to the oral formulations in ten patients with a 100% eradication rate of *H. pylori* versus 30% when omeprazole IV was used alone during the three-day period.[54]

In further studies of dual therapy, other antimicrobial agents have also been combined with omeprazole. It has been found that the theory of "anacidity enhanced antibiotic therapy" cannot unconditionally be applied to other antibiotics.[49] Clarithromycin is an antimicrobial though, that may be of value in combination with omeprazole.[55,56,57] Katelaris et al compared clarithromycin 500 mg three times daily to amoxicillin in combination with omeprazole, and concluded that dual treatment with clarithromycin caused a slightly higher eradication rate (72% versus 69.2%). However, due to a higher incidence of side effects and cost, it should be considered an alternative and not a first line agent.[57] No eradication of *H. pylori* was observed post treatment with omeprazole and itraconazole.[58]

Triple therapy regimens with clarithromycin, metronidazole and either omeprazole or ranitidine have achieved high eradication rates[63,64] and gastroenterologists appear to have favoured one of these combinations in 1996.

Study results for dual therapy including omeprazole are outlined in Table II. It therefore can be concluded that although dual therapy described here is not quite as

Table II: Eradication Rates using Different Regimens Containing Omeprazole

DRUG(S)	ERADICATION	DURATION	REFERENCES
omeprazole, amoxicillin			
begun at the same time	>80%	14 days	5
	82.8%	14 days	49
	83%	14 days	38
	69.2%	14 days	57
	61%	7 days	49
with 7 day omeprazole pretreatment	28%	7 days	49
with 3 day omeprazole pretreatment	30%	14 days	54
omeprazole, clarithromycin	80%	14 days	56
	72%	14 days	57
	82%	7 days of omep 5 days of clar	59
omeprazole	4%	28 days	44
	0%	14 days	49
amoxicillin	23%		3
	23%		40
	0%		60

> -greater than, as determined by the NIH Consensus Development Panel [5]

effective as the conventional triple therapy, it has higher patient acceptance with fewer treatment-limiting side effects. Cost differences with dual and triple therapy are indicated in Table III.

Investigations into future treatments include the use of treatment immunization for *H. pylori* associated ulcers.[61] Other modalities could involve the use of IgA antibodies against *H. pylori* or of receptor analogues preventing the adherence of the organism to epithelial cells.[28]

SUMMARY

In conclusion, it is important to consider which patients are good candidates for *H. pylori* treatment as part of peptic disease therapy. Whereas antibiotic therapy in PUD used to be reserved for patients with persistant or recurring duodenal or gastric ulcers (two or more episodes), it now involves a much larger group.[62] In February 1994, a consensus meeting by the National Institutes of Health recommended that all patients with *H. pylori* infection and peptic ulcer disease, whether initial or recurrent, as well as those already receiving antisecretory agents, should receive antimicrobial treatment.[21] This also includes individuals who are taking NSAIDs, which whenever possible, should be discontinued.[5] These treatment recommendations do not extend to persons with non-ulcer dyspepsia, those with *H. pylori* infections who are asymptomatic, nor for the use in cancer prevention.[21]

Triple therapy with bismuth had been the treatment of choice for the eradication of *H. pylori*, but with more information becoming available in the treatment involving omeprazole with amoxicillin or clarithromycin and the promising results, therapy is changing. Treatment should be tailored to the individual patient. Although, there is no definitive protocol to the eradication of *H. pylori*, one approach is outlined Table III. This treatment plan suggests initiating with a two-drug combination and advancing to a three-drug combination if the former is ineffective, either due to resistance or intolerance to any of these agents. Also, currently a 14-day treatment course is recommended for any regimen.

Although treatments outlined in this paper have provided good results, the search for a more ideal drug regimen for the eradication of *H. pylori* continues at a fast pace. Hence the current recommendations may quickly be superceded as new data become available.

Table III: Approaches to Eradicating Helicobacter Pylori Infection

Dual therapy			
Omeprazole (15 min. before meals)	20mg bid	days: 1-14	cost: $67.92
+	or 40 mg qd	1-14	
Amoxicillin (30 min. after meals)	500mg qid	1-14	
	or 1000mg bid	1-14	
Omeprazole			
+			
Clarithromycin (with meals)	500mg tid	1-14	$181.82
If double therapy is ineffective:			
Triple therapy			
bismuth subsalicylate	624mg qid	1-14	$25.81
metronidazole	250mg qid	1-14	
tetracycline	500mg qid	1-14	
If patient is allergic/intolerant to tetracyline: substitution of tetracyline with			
-amoxicillin	500mg tid	1-14	$27.95
If metronidazole resistant H. pylori: substitution of metronidazole with			
-amoxicillin	500mg tid	1-14	$28.24
-or erythromycin base	500mg qid	1-14	$92.35
+ omeprazole	20mg bid	1-14	

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