Current therapy for *Helicobacter pylori* infection in children and adolescents

Benjamin D Gold MD

BD Gold. Current therapy for *Helicobacter pylori* infection in children and adolescents. Can J Gastroenterol 1999; 13(7): 571-579. *Helicobacter pylori* infects approximately 50% of the world's population and is a definitive cause of gastroduodenal disease (ie, gastritis, duodenal and gastric ulcers) in children and adults. Four consensus conferences held around the globe have brought together clinicians, scientists, epidemiologists and health care economists to discuss the role of the gastric pathogen *H pylori* in human gastroduodenal disease. At each of these conferences, the overriding objective was to reach a consensus on the development of practical guidelines for the diagnosis and treatment of *H pylori*-infected individuals. However, it was not until the Canadian *H pylori* Consensus Conference, held in November 1997, that the issues of *H pylori* infection in children were addressed. Therapies for *H pylori* infection in children, presented in part at the First Canadian Pediatric *H pylori* Consensus Conference, held in Victoria, British Columbia, November 1998, are reviewed in this paper.

Key Words: *Children; Eradication;* Helicobacter pylori; *Infection*

Traitement actuel de l'infection à *Helicobacter pylori* chez les enfants et les adolescents

RÉSUMÉ : *Helicobacter pylori* est présent chez environ 50 % de la population mondiale et est une cause établie de maladie gastroduodénale (p. ex., gastrite, ulcères duodénaux et gastriques) chez les enfants et les adultes. Quatre conférences consensuelles tenues dans le monde ont réuni des médecins, des chercheurs, des épidémiologues et des économistes de la santé pour qu'ils débattent du rôle de cet organisme pathogène dans la maladie gastroduodénale chez l'être humain. À chacune de ces conférences, l'objectif principal était de s'entendre sur la mise au point de directives pratiques pour le diagnostic et le traitement des sujets infectés par *H. pylori*. En revanche, ce n'est pas avant la tenue de la Conférence consensuelle canadienne sur *H. pylori*, tenue en novembre 1997 que les questions entourant l'infection à *H. pylori* chez les enfants ont commencé à être débattues. On passe ici en revue les traitements contre l'infection à *H. pylori* chez les enfants, présentés en partie lors de la I^{re} conférence consensuelle canadienne sur l'infection à *H. pylori* chez l'enfant, tenue à Victoria, en Colombie britannique, en novembre 1998.

EPIDEMIOLOGY OF ULCERS

To provide an evidence-based discussion on traditional therapy for *Helicobacter pylori* infection and develop recommendations on treatment guidelines, the prevalence and health care impact of peptic ulcer disease and the pathogenesis of ulcers in children must first be considered. Peptic ulcer disease causes significant morbidity and mortality in adults (1). Studies have yet to be performed that evaluate both the overall prevalence of peptic ulcer disease and the health care impact of this condition in children. Anecdotal reports suggest that ulcer frequency in children may be increasing, and multicentre studies may contribute to a better understanding of the prevalence and economic impact of this disorder in the pediatric population (2,3).

We have employed the Pediatric Hospital Information System, a database of over 21 pediatric hospitals in the United States, to determine the prevalence of peptic ulcer disease in hospitalized children (unpublished data). Of 522,068 hospital discharges from October 1995 through December 1997, 3586 (0.7%) were for peptic ulcer disease or gastritis/duodenitis; of these, 1297 (268 ulcers, 1029 gastroduodenal inflammation) were the child's primary diagnoses. Overall, 29% of patients with these diagnoses had an *H pylori* test performed in the hospital; testing increased from 17% in 1995 to 34% in 1997 ($P<0.005$). The median age of patients with a primary diagnosis of peptic ulcer disease was nine years (range less than one year to 17 years); 52% were white, 26% were black and 60% were boys. Fifty-four per

Division of Pediatric Gastroenterology and Nutrition, Department of Pediatrics, Emory University School of Medicine; Helicobacter Laboratory, Foodborne and Diarrheal Diseases Branch, DBMD, NCID, Centers for Disease Control and Prevention, Atlanta, Georgia, USA

Correspondence and reprints: Dr Benjamin D Gold, Associate Professor of Pediatrics and Microbiology, Division of Pediatric Gastroenterology and Nutrition, Department of Pediatrics, Emory University School of Medicine, 2040 Ridgewood Drive NE, Atlanta, Georgia 30322 USA. Telephone 404-727-4036, fax 404-727-2120, e-mail ben_gold@oz.ped.emory.edu

cent of those with ulcers had hemorrhage, and only 17% of these had documented *H pylori* infection. In comparison, 27% of those with inflammation had hemorrhage, and 6% had proven *H pylori* infection. Of the 268 ulcer cases, 92 (34%) were duodenal ulcers and 136 (51%) were gastric ulcers. Overall, *H pylori* infection was diagnosed in 39% of those with duodenal ulcer and 15% of those with gastric ulcer. However, this number may be artifactually low due to both the low levels of testing, and the poorly validated and inaccurate tests employed to diagnose *H pylori* infection. Additionally, because the International Classification of Diseases code for *H pylori* was only instituted in hospitals in the United States in 1995, these results are likely to provide a gross underestimation of the percentage of peptic ulcers that are associated with childhood infection with *H pylori*. These data indicate that multicentre epidemiological studies of pediatric patients in the outpatient setting are needed to determine both the impact of ulcer disease and the frequency of associated *H pylori* infection in children, and thereby establish relevant treatment guidelines.

PATHOGENESIS OF ULCERS

Treatment guidelines are best developed from an understanding of the pathobiology of gastroduodenal inflammation and ulceration. Ulcers of the duodenum or stomach have historically been classified as either primary or secondary (4). Secondary gastroduodenal ulcers generally occur due to a systemic condition such as overwhelming sepsis or as a result of drug ingestion (ie, nonsteroidal anti-inflammatory agents) (5). Secondary gastric or duodenal ulcers can also occur in specific diseases such as Zollinger-Ellison syndrome and Crohn's disease (6,7) or in other diseases such as cystic fibrosis and sickle cell disease (8). Secondary ulcers, unlike primary ulcers, also can be distinguished by history on initial evaluation of the child with suspected ulcer disease because children with secondary ulcers typically do not have a family history of peptic ulcer disease.

Children presenting with duodenal or gastric ulcers and having no other identified etiologies most likely have primary gastroduodenal ulceration. In the majority of patients, mucosal inflammation and ulceration are caused by the spiral-shaped, Gram-negative, microaerobic bacillus, *H pylori*. However, recent reports suggest that there may be a subset of up to 20% of children with *H pylori*-negative duodenal or gastric ulcers (9).

A reduction in peptic ulcer disease in both adults and children is necessary to control associated health care costs as well as to reduce human morbidity and mortality. Highly efficacious and economical treatment regimens are needed. Targeted therapy must, therefore, focus on the elimination of aggressive factors, including *H pylori*.

The outcome of gastroduodenal disease after *H pylori* colonization is believed to be a result of both host and bacterial determinants (3,10). One of the aggressive factors implicated in the pathogenesis of mucosal ulceration in the duodenum is acid. For decades, the mainstay of treatment for duodenal ulcers has been acid reduction. However, the discovery of *H pylori* has had a tremendous impact on our understanding of gastric physiology and has changed the approach to developing efficacious strategies for ulcer elimination (11).

The effect of *H pylori* on gastric acid secretion is controversial. In particular, the effect of *H pylori* on acid secretion in children remains poorly defined. One recent study demonstrated that acid secretion differs between children with gastric ulcers and those with duodenal ulcers (12). Using 24 h pH measurements as a determinant of acid secretion, these authors reported that gastric acidity is reduced in children with primary gastric ulcers (ie, *H pylori*-associated) but is increased to above adult levels in children with duodenal ulcers (12). However, the majority of adult studies are equivocal – maximal acid output or basal acid output values over a 24 h period are not predictive of the likelihood of ulcer development.

Recent studies demonstrate that there is impaired bicarbonate production in the proximal duodenum of *H pylori*-infected adult patients with duodenal ulcers (13). Additional studies of gastric acid production and duodenal bicarbonate secretion in *H pylori*-infected and uninfected children are needed to establish more directed and efficacious therapeutic strategies.

Inflammation of the stomach and duodenum in both humans and ferrets as a result of helicobacter infection is associated with a concurrent decrease in gastroduodenal mucosal surface hydrophobicity, believed to be due to a disturbance in the overlying mucous layer (14,15). Evidence points to disturbances in the gastroduodenal mucous layer in ulcer pathogenesis, but studies have yet to be done in children.

H PYLORI AS A GASTRIC PATHOGEN IN CHILDREN: HISTORICAL LANDMARKS

When discussing treatment guidelines for *H pylori* infection in children it is important to have a historical perspective of the evidence supporting the role of this organism as a gastric pathogen in humans. The paramount papers reporting the discovery of *H pylori* (then *Campylobacter pylori*) and its causative role in gastroduodenal mucosal inflammation in humans came from studies of infected adults (16). However, reports of gastric mucosal inflammation associated with infection by this organism in children followed closely thereafter. Four landmark pediatric papers appeared in the literature within six months of each other (17-20), beginning in 1986 with Hill and colleagues (17). In each of these four reports, the investigators described the association of gastric colonization by *H pylori* with inflammation and/or ulceration of the duodenal or gastric mucosa (17-20). Moreover, although the specifics of the therapeutic specimens used were not clearly described, all of the authors described a resolution of the gastroduodenal inflammation in the child following eradication of the organism.

Subsequently, there have been four major meetings, termed consensus conferences, in which experts from around the world (ie, gastroenterologists, infectious diseases specialists, microbiologists, epidemiologists and health economists)

examined the role of *H pylori* in gastroduodenal disease in humans and then developed guidelines based on a summary of the evidence (21-26). However, clinical practice guidelines and a summary of evidence for *H pylori* infection in children were left for future conferences to address.

In the late autumn of 1997, a group of experts convened for a Canadian consensus conference from which the very first recommendations for children infected with *H pylori* were offered (25). The Canadian recommendations were similar to those of the previous three consensus meetings for the implementation of therapy for *H pylori*-infected adults. However, this group made the following recommendations for the *H pylori*-infected child. Based on the evidence available, it was recommended that noninvasive testing by serology or urea breath testing were not indicated in a child presenting with abdominal pain. Empirical therapy of suspected *H pylori* infection and the treatment of a child with a positive serological test for *H pylori* were also not indicated. This group of experts felt that if suspicion of a peptic ulcer is high, a child should be endoscoped with gastric biopsies taken for both delineation of the ulcer or mucosal disease, and confirmation of *H pylori* infection.

DIAGNOSTIC TESTS FOR *H PYLORI* INFECTION

To initiate eradication therapy for *H pylori* infection in children, accurate diagnosis of active infection is critical. Therefore, it is important to understand the accuracy of available diagnostics tests and their limitations. There are two general categories of tests for *H pylori* infection – those that use upper gastrointestinal endoscopy and biopsy (invasive tests), and those that use breath, blood, urine or stool samples to detect the presence of infection (noninvasive tests). Histology is deemed the gold standard test for the diagnosis of *H pylori* infection (27-29).

Endoscopy with multiple biopsies enables diagnostic accuracy to detect *H pylori* infection and gastroduodenal disease sequelae by providing information regarding the presence or absence of mucosal ulceration, and characterization of the severity and topographic distribution of gastritis, the presence of atrophic gastritis and intestinal metaplasia, and the presence of mucosa-associated lymphoid tissue (MALT) lymphoma (30,31). Endoscopy also provides information about other upper gastrointestinal mucosal disorders such as peptic esophagitis, which may be the underlying cause of the patient's symptoms (29,30). Finally, endoscopy and biopsy allow *H pylori* to be cultured for antibiotic resistance testing; a particularly important clinical tool for eradication therapy failures. Endoscopy, although easily performed in referral centres across North America in children, is an 'invasive' procedure requiring heavy sedation or anesthesia. In addition, there is limited availability of endoscopy for children residing outside major urban centres, and it can be an expensive diagnostic procedure.

The use of urease breath testing in children is increasingly employed as a clinical tool for the diagnosis of *H pylori* infection. Breath testing, which uses either a radioactive isotope (^{14}C-labelled urea) or stable, nonradioactive isotope (^{13}C) is an exquisitely sensitive and specific noninvasive test both in adults (32) and children (33,34). In addition, the accuracy of the test has been proposed to correlate with bacterial load in children (34,35). Breath testing can be cumbersome and technically more difficult to perform, particularly in the very young (those under two years of age). The ^{13}C-urea breath test is moderately expensive (compared with serology, for instance) and, at present, has limited availability for children because the test parameters have either not been standardized or are laboratory specific (36). In all age groups, urease breath testing is affected by antibiotics, acid-suppressing medications and other urease-secreting organisms (37).

The use of blood to detect immunoglobulin G (IgG) antibodies to *H pylori* as an indicator of current or past infection with *H pylori* has been widely exploited by industry with a multitude of purported commercial uses in children. However, compared with histology, the accuracy of most commercial immunoassays to detect the presence of *H pylori* infection is poor unless they are used in populations in which they were developed (38,39). Clearly, age-related cutoff values for commercial serological and whole blood tests to detect *H pylori* infection have not been established for children (40). More importantly, serological tests cannot be used to verify eradication because IgG antibodies can persist for prolonged periods after endoscopically proven eradication of *H pylori* (40).

WHAT CONDITIONS HAVE EVIDENCE-BASED JUSTIFICATION FOR INITIATING TREATMENT OF *H PYLORI*?

Most critical to recommendations for traditional therapeutic guidelines for the *H pylori*-infected child is a review of the available evidence supporting conditions that require treatment (21-25). When critically reviewing the literature regarding the specific conditions associated with *H pylori* infection in which the evidence is strongest favouring eradication therapy, a number of clinical settings clearly have evidence-based criteria for the initiation of eradication therapy. There is compelling evidence that peptic ulcer disease is an important clinical manifestation of *H pylori* infection. Therefore, eradication therapy is warranted in children with *H pylori* infection and documented peptic ulceration. It is clear that successful eradication of *H pylori* results in a permanent cure of ulcer disease and a lifetime free from medications (24). Although there are no multicentre, randomized, controlled treatment trials evaluating the efficacy of *H pylori* eradication on ulcer disease in children, the data are quite compelling in favour of eradication in these patients (41).

At least two recent studies have shown that *H pylori* eradication prevents intestinal hemorrhage at one year of follow-up (42,43). Although frank bleeding from ulcers is an uncommon event in childhood, the evidence from adults warrants *H pylori* eradication therapy in such patients at any age.

A number of uncontrolled studies of small sample size show complete or partial regression of MALT lymphoma af-

TABLE 1
Agents that inhibit *Helicobacter pylori* in vivo

Antibiotic resistance	No Antibiotic resistance
Metronidazole	Colloidal bismuth subcitrate
Tinidazole	Bismuth subsalicylate
Erythromycin base	Tetracycline
Clarithromycin	Doxycycline
Ciprofloxacin	Furazolidone
Ofloxacin	Nitrofurantoin
Norfloxacin	
Amoxicillin or ampicillin	

TABLE 2
Primary resistance to nitroimidazole compounds

Country	Number of strains	Resistance (%)	Methodology
Belgium	206	27	Breakpoint method
Finland	559	26	Disc diffusion test
France	97	41	E test
Ireland	189	28	Agar dilution test
The Netherlands	140	7	Disc diffusion test
Europe	443	28	E test
Multinational study			
Belgium	54	24	E test
Finland	50	34	E test
France	23	25	E test
Greece	39	49	E test
Ireland	35	20	E test
Italy	25	24	E test
Portugal	50	26	E test
Spain	15	7	E test
Sweden	50	14	E test
The Netherlands	33	38	E test
United Kingdom	44	20	E test
United States	25	24	Agar dilution
Australia	100	17	Agar dilution
Asia			
Malaysia	37	11	Disc diffusion test
Bangladesh	22	95	Disc diffusion test
Africa			
Zaire	32	84	Breakpoint test
Burkina Faso	35	77	E test

In a study by EJ van der Wouden et al (87) , 1037 isolates were evaluated from 1993 to 1996 by disc diffusion and E test. Metronidazole resistance increased from 7% to 32% in the three-year period

ter eradication of *H pylori* infection, including that in children (44-46). In addition, the evidence favouring the etiological role of *H pylori* in the development of MALT lymphoma is compelling. However, there are no randomized, controlled clinical trials showing that successful eradication of *H pylori* results in regression and disappearance of MALT lymphoma. Because this is a relatively rare tumour, the biology of which is still unclear, it may be difficult to acquire such evidence in a timely fashion, particularly in children. However, at least two of the consensus conferences have agreed that the best available evidence dictates the initiation of *H pylori* eradication therapy to treat low grade MALTomas (22,25).

A recent meta-analysis of the literature by Macarthur et al (2) concluded that recurrent abdominal pain, at least as defined by Apley, is not associated with *H pylori* infection. Therefore, it has been recommended that treatment not be indicated in the child who has recurrent abdominal pain and suspected *H pylori* infection. However, the literature remains controversial regarding the issue of nonulcer dyspepsia (NUD). Whether eradication therapy has any effect on the resolution of symptoms in this clinical setting is unresolved. Even when defining NUD as upper gastrointestinal symptoms where upper gastrointestinal endoscopy has been performed and no ulcer has been visualized, the data supporting eradication of *H pylori* to relieve clinical symptoms are still equivocal (47).

The evidence is even less definitive in children; up to 40% have been reported to continue to have abdominal pain in the face of *H pylori* eradication (48). Moreover, there are few validated and reproducible 'quality of life' measures or symptom scoring instruments that can be employed as a reliable outcome measure for evaluating the success or failure of eradication therapy in a child with abdominal pain and *H pylori* infection. It is critical to develop such tools for use in multicentre, collaborative efforts among pediatric centres to answer these unresolved questions.

HOW IS SUCCESSFUL THERAPY FOR PEDIATRIC *H PYLORI* INFECTION DETERMINED?

A paucity of studies have critically evaluated the question of the end points, goals or desired outcomes of therapy. These considerations must be taken into account when developing guidelines or eradication therapy of *H pylori* infection in children. A regimen should be the optimum treatment protocol that is tolerable, safe, simple to use and associated with high compliance, and that can be used in a child. For example, varying treatment end points may direct the choice of treatment regimen. Should the end point be the eradication of *H pylori*? If so, what method should be used as the 'test for cure'? Alternatively, could the intent to treat be for the purpose of resolving gastroduodenal disease or clinical symptoms, which would require varying monitors of outcome?

Patient compliance appears to be the single most important factor influencing the success of therapy (49). Compliance is influenced by the simplicity of the treatment regimen and tolerability (ie, the frequency of side effects). The frequency of side effects ranges from 15% to 73% depending on the regimen employed (49,50). Compliance decreases with increasing length of the treatment regimen, reducing drug dosing intervals and the frequency of side effects (51).

Antimicrobial resistance of infecting *H pylori* strains is another important factor (Tables 1-4) that appears to be influenced by patient compliance and use of antibiotics for other disorders (eg, metronidazole for treating parasitic in-

TABLE 3
Clarithromycin resistance of *Helicobacter pylori* strains

Country	Number of strains	Resistance (%)	Methodology
Europe			
France	97	9	E test
Belgium	18	11	Agar dilution
The Netherlands	68	3	Disc diffusion
Switzerland	11	0	Disc diffusion
Africa			
Burkina Faso	35	14	E test
United States	37	11	Agar dilution
Australia	108	2	Disc diffusion

TABLE 4
Resistance of pediatric *Helicobacter pylori* strains

State	Number of strains tested	Resistance (mean %)	Drug
Georgia	15	5	Clarithromycin
		20	Metronidazole
Alabama	4	25	Metronidazole
Florida	12	25	Clarithromycin
		60	Metronidazole
		1	Amoxicillin
South Carolina	3	33	Metronidazole
Ohio	10	10	Metronidazole

fections in children and vaginal infections in women) (52). Another difficulty in devising an optimal treatment for the eradication of *H pylori* infection is the acquisition of resistance. *H pylori* appears to acquire resistance to certain antimicrobial drugs easily, such as imidazole derivatives (53-55) and quinolones (52,56). Therefore, antibiotics should not be used as monotherapy. This is of particular importance in underdeveloped areas with a high prevalence of *H pylori* infection, where these drugs are frequently used for the treatment of other conditions, and *H pylori* strains have been shown to have high prevalence of resistance (52).

WHO SHOULD BE TREATED FOR *H PYLORI* INFECTION?

Serological, salivary and urinary testing for *H pylori*, whether ordered by the primary care physician (family practitioner or pediatrician) or the pediatric gastroenterologist, should not be used to decide treatment initiation. This is because the accuracy of available commercial assays are suspect in the pediatric age group. Urea breath testing may be used as a noninvasive diagnostic test that, if found positive, warrants the initiation of *H pylori* eradication therapy. However, the following caveats should be considered: controlled trials of breath testing with establishment of proper cutoff values in children of a variety of ages and in a number of community settings are necessary; and upper endoscopy should be performed if clinical signs and symptoms (eg, anemia, hematochezia) dictate that it is necessary to determine gastric and duodenal pathology. Children who are diagnosed with *H pylori* infection and a gastric ulcer or duodenal ulcer at endoscopy should be treated to eradicate the gastric infection. A child with biopsy-proven gastritis with histological evidence of *H pylori* infection by upper endoscopy should be considered for treatment with eradication therapy and follow-up management performed on a case-by-case basis. However, the data supporting treatment of *H pylori* infection in children with gastritis alone are still not definitive. Patients who have failed empirical acid blockade therapy (ie, H_2 receptor antagonists and proton pump inhibitors [PPIs]), should be evaluated for *H pylori* infection before the initiation of eradication therapy. If a child has a previously documented ulcer (gastric or duodenal by upper gastrointestinal series) and is found to be *H pylori* seropositive, the evidence does not indicate that treatment is warranted. These children should be evaluated by upper gastrointestinal endoscopy to confirm the presence of the ulcer and *H pylori* infection. The rare children with endoscopically proven MALT lymphoma and *H pylori* infection should be treated with *H pylori* eradication therapy. Further studies of pediatric patients with MALT lymphoma need to be performed to monitor recurrence, progression or remission of the tumour, and to determine successful eradication of *H pylori* infection. Children who are undergoing maintenance antisecretory therapy and are subsequently diagnosed with *H pylori*-associated peptic ulcer disease should be treated for their infection, regardless of whether they are suffering from the initial disease presentation or from a recurrence.

Controlled prospective studies are needed to assess the benefits of treating children with *H pylori* infection who have NUD or recurrent abdominal pain, reside in chronic care facilities (asymptomatic or symptomatic), or have a family member who is infected with *H pylori* or has peptic ulcer disease or gastric cancer.

ACID SUPPRESSION FOR PEPTIC ULCER DISEASE IN *H PYLORI*-INFECTED CHILDREN IS JUST NOT ENOUGH

H_2-receptor antagonists: Blanco et al (57) treated 59 patients with *H pylori*-associated gastric or duodenal ulcers with H_2-receptor antagonists for up to eight weeks. While these drugs healed the peptic ulcer in all patients, *H pylori* remained present in all patients, associated with chronic inflammation of the gastric mucosa. Similar findings have been observed by at least four other groups (58-61).

PPIs: Although it has been observed that a PPI can clear *H pylori* temporarily from the antrum when given as monotherapy (62), omeprazole does not eradicate *H pylori* infection (63). Conversely, during a transient period of 'antral clearance', increased activity of *H pylori*-associated gastritis is observed in the corpus mucosa (62,64). However, the combination of a PPI and certain antibiotics, especially amoxicillin and clarithromycin, has proved to be a highly ef-

fective therapy against *H pylori* colonization of the gastric mucosa (65). Eradication rates of above 90% have been obtained by several investigators by using intention to treat criteria (24,65).

Although it is unclear how omeprazole enhances the effect of antibiotics, two theories have been advanced. As an organism that has evolved to live in an acid microenvironment, *H pylori* may have some ecological requirement for a small amount of acid (66). In patients with long standing chronic gastritis in which hypochlorhydria has supervened, *H pylori* becomes less prominent and may even disappear (67). This suppressive activity of decreased acidity may render the organism more vulnerable to the effects of an antibiotic. Alternatively, certain antibiotics, in particular amoxicillin, are increasingly active as the pH increases. A combination of these two factors may be responsible for the effective results obtained in humans.

H PYLORI TREATMENT REGIMENS

Combination therapies: Successful therapy for *H pylori* is based on an antibacterial agent that acts luminally to cause significant suppression of the bacterium. A second agent acting both topically and systematically is more efficacious and less likely to promote the selection of resistant isolates. Amoxicillin has been widely used to treat *H pylori*, especially in combination with bismuth (68). A disadvantage of amoxicillin is a 5% incidence of *Clostridium difficile*-induced colitis, which may be prevented by combining the drug with metronidazole (69). This regimen was advocated as a seven-day treatment by Logan et al (69), with an overall eradication rate of 74%.

Others have observed *H pylori* eradication in up to 70% of patients given combination dual therapy with amoxicillin and omeprazole (70). It is proposed that omeprazole enhances antibiotic penetration into a pH neutral location (ie, between parietal cells where *H pylori* tends to colonize). Preliminary results from a larger study using the combination amoxicillin-omeprazole demonstrated an eradication rate of 80% (71). A recent trial investigated the effect of a clarithromycin and omeprazole combination therapy in 73 patients with *H pylori*-associated gastroduodenal pathology (69). A negative ^{13}C-urea breath test determined that *H pylori* was cleared after two weeks of treatment in 95.9% of the patients and eradicated in 78.1%.

Triple therapies have the advantage of both luminal and systemic activity. Luminally active agents against *H pylori* are bismuth, tetracycline, amoxicillin, clarithromycin and furazolidone (71,72). Most triple therapies contain a nitroimidazole (eg, metronidazole), which appears to be the most active component against *H pylori*, provided that bacterial suppression with the other agents has occurred. The combination of bismuth, tetracycline and metronidazole seems to be particularly effective (73). One study demonstrated a 90% eradication rate, suggesting that metronidazole-resistant strains are eradicated by this triple therapy (74). Further support is provided by a recent comparison of combination therapies for metronidazole-resistant organisms, in which the eradication rate exceeded 50% (73). Because the eradication rate is low using dual tetracycline and bismuth therapy, it appears that synergism exists between metronidazole and the other drugs (73).

Bazzoli and colleagues (75) reported an eradication rate of 100% of *H pylori* in 36 patients treated with a one-week regimen of omeprazole, clarithromycin and tinidazole. These results were later confirmed with follow-up eradication rates of 95% (76). Furthermore, the bacterial eradication rate decreased markedly after substitution of nitroimidazole by tetracycline (77), suggesting that nitroimidazoles are important to include in treatment options that confer high rates of bacterial eradication.

A recent multicentre adult study using clarithromycin, omeprazole and amoxicillin for one week obtained an eradication rate of 96% (78). Because of the short duration and excellent eradication rate of this triple therapy, such a treatment should be considered the first choice for use in the initial treatment and eradication of *H pylori* in both adults and in children (79).

Adverse effects are primarily caused by the antibiotics employed in the anti-*H pylori* therapy regimens (65). Despite the success of *H pylori* eradication using triple therapy combinations of a bismuth compound, metronidazole, and either amoxicillin or tetracycline, these options produce an increased risk of adverse reactions (80). Adverse reactions in turn lead to noncompliance, which results in treatment failure and acquired antibiotic resistance. Frequently reported adverse reactions are gastrointestinal complaints that can lead to discontinuation of therapy. Triple therapy increases the incidence of adverse events with up to 20% of study patients withdrawing from treatment (81). Bismuth compounds may also cause adverse reactions, although less commonly than antibiotics (82). Bismuth toxicity with compounds such as bismuth subsalicylate and colloidal bismuth subcitrate is rare and can be avoided by proper use; intake should be limited to a period of no more than four weeks and treatment should be avoided in the presence of renal insufficiency (82).

Patient compliance in taking prescribed medications depends on a number of factors including severity of symptoms, number and quantity of drugs taken, duration of treatment, complexity of the treatment regimen and drug-related adverse effects (82). Graham et al (49) demonstrated a lack of compliance as the main cause for eradication failure when using triple therapy regimens.

In this study, age, sex, type of gastrointestinal disease, duration of therapy and the amount of bismuth had no effect on the eradication rate. However, *H pylori* was eradicated in 96% of the patients who took more than 60% of the prescribed medication, but in only 69% of patients who took less than 60% of the drugs.

Compliance also may be reduced by the rapid resolution of abdominal pain, as a consequence of antiulcer therapy (49,50). If patients discontinue the prescribed medications when symptoms disappear, they will not complete the treatment course required to eradicate their *H pylori*. Because

compliance seems to be a major factor in the successful treatment of *H pylori* infection, it is of no surprise that investigators have tried to eradicate *H pylori* with shorter courses of combination therapy (83). However, to date, the optimal duration of therapy has still not been determined.

TREATMENT OPTIONS FOR *H PYLORI* INFECTION IN CHILDREN

Four categories of eradication regimens have been used to treat *H pylori* infection.

- **Metronidazole-containing regimens:** Metronidazole + bismuth + tetracycline + H_2 receptor antagonist; metronidazole + amoxicillin + H_2 receptor antagonist.
- **Clarithromycin-containing regimens:** Clarithromycin + PPI; clarithromycin + amoxicillin + PPI.
- **Metronidazole and clarithromycin-containing regimens:** Metronidazole + clarithromycin + PPI, metronidazole + clarithromycin + ranitidine bismuth citrate (RBC).
- **Bismuth-containing (H_2 receptor antagonist and bismuth) regimens or neither metronidazole nor clarithromycin-containing:** Amoxicillin + PPI.

Eight regimens have been approved in the past year by the United States Food and Drug Administration (FDA) (as of July 24, 1998) (78). All treatment regimens are given for 10 days to two weeks with cure rates of 63% to 96% reported. The eight regimens are (84):

- Omeprazole 40 mg/day + clarithromycin 500 mg tid for two weeks, then omeprazole 20 mg/day for two weeks.
- RBC 400 mg bid + clarithromycin 500 mg tid for two weeks then RBC 400 mg bid for two weeks
- Bismuth subsalicylate (Pepto Bismol, Proctor and Gamble, Cincinnati, Ohio) 525 mg qid + metronidazole 250 mg qid + tetracycline 500 mg qid for two weeks + H_2 receptor antagonist therapy as directed for four weeks.
- Lansoprazole 30 mg bid + amoxicillin 1 g bid + clarithromycin 500 mg bid for 10 days.
- Lansoprazole 30 mg tid + amoxicillin 1 g tid for two weeks.
- RBC 400 mg bid for four weeks + clarithromycin 500 mg bid for the first two weeks.
- Omeprazole 20 mg bid for 10 days + clarithromycin 500 mg bid for 10 days + amoxicillin 1 g bid for 10 days.
- Lansoprazole 30 mg bid + clarithromycin 500 mg bid + amoxicillin 1 g bid for 10 days.

The best available evidence indicates that there are six potential treatment options for *H pylori* infection in children (Table 5). The proposed pediatric treatment options listed in Table 5 have not yet been approved by the FDA for use in children at the time of publication. Dual therapy-containing regimens have not been offered as options due to the clear superiority of triple therapy-containing regimens in studies of adults and small series of children (85,86). In addition, the RBC-containing regimens that are FDA-approved for use in adults are not included due to a lack of published studies on this regimen's use in children.

TABLE 5
Treatment options for the eradication of *Helicobacter pylori* in children

Regimen
Proton pump inhibitor (eg, omeprazole 1 mg/kg/day up to 20 mg bid or lansoprazole 1.5 mg/kg/day up to 30 mg bid or pantoprazole 2.0 mg/kg/day up to 40 mg bid + amoxicillin 50 mg/kg/day up to 1 g bid + clarithromycin 15 mg/kg/day up to 500 mg bid for 7 to 14 days
Proton pump inhibitor + amoxicillin + metronidazole 20 mg/kg/day up to 500 bid for 7 to 14 days
Proton pump inhibitor + clarithromycin + metronidazole for 7 to 14 days
Proton pump inhibitor + amoxicillin + tetracycline 50 mg/kg/day up to 1 g bid for 7 to 14 days (only for children older than 8 years of age)
Second line options available for use both in treatment failures and, possibly, as initial therapy for children from regions of the world where primary resistance to metronidazole is high:
Bismuth subsalicylate 1 tablet (262 mg) qid or 15 mL (17.6 mg/mL) qid + proton pump inhibitor + metronidazole + tetracycline or amoxicillin or clarithromycin for 7 to 14 days
Bismuth-ranitidine (1 tablet bid) + clarithromycin + metronidazole for 7 to 14 days

Note: regimens are not listed in order of eradication rates and efficacy

CONCLUSIONS

There is a need to develop a proven, efficacious treatment for *H pylori* infection in children. If it is accepted that gastric colonization by *H pylori* is associated with pediatric gastroduodenal disease, then eradication of the organism must be the intent of the practitioner caring for the *H pylori*-infected child. Therefore, the desired outcome for individuals caring for these children should be to eradicate *H pylori* by therapy that has few or no adverse effects, accompanied by the resolution of symptoms with resultant resumption of functional health.

There is an important discrepancy between the in vitro results of antimicrobial drugs on *H pylori* and their in vivo effect on the organism. This discrepancy results in the design of most therapeutic trials based upon empirical considerations. In addition, the organism readily develops resistance against a great number of drugs, especially if they are administered as monotherapy. Finally, no randomized, controlled treatment trials have been performed in children infected with *H pylori*. For all these reasons, an ideal treatment for *H pylori* in children has yet to be determined. Current *H pylori* eradication therapy recommendations have been made by extrapolating findings from adult studies in combination with data available from small case series reported in pediatric patients. Multicentre collaborative treatment trials of *H pylori*-infected children are critically needed. Only in this manner can evidence-based practice guidelines for *H pylori* infection in children be established.

ACKNOWLEDGEMENTS: Dr Gold is supported in part by a grant from the National Institutes of Health, NIDDK ROI-53708-01

REFERENCES

1. Sonnenberg A. Factors which influence the incidence and the course of peptic ulcer. Scand J Gastroenterol 1988;23:119-40.
2. Macarthur C, Saunders N, Feldman W. *Helicobacter pylori*, gastroduodenal disease, and recurrent abdominal pain in children. JAMA 1995;273:729-34.
3. Gold BD. *Helicobacter pylori* infection and peptic ulcer disease. Semin Pediatr Infect Dis 1996;7:265-71.
4. Drumm B, Gormally S, Sherman PM. Gastritis and peptic ulcer disease. In: Walker AW, Durie PR, Hamilton JR, Walker-Smith J, eds. Pediatric Gastrointestinal Disease: Pathophysiology, Diagnosis and Management, vol 1. St Louis: BC Decker, 1996:506-18.
5. Kurata JH, Nogawa AN. Meta-analysis of risk factors for peptic ulcer disease: nonsteroidal anti-inflammatory drugs, *Helicobacter pylori*, and smoking. J Clin Gastroenterol 1997;24:2-17.
6. Hirschowitz BI. Zollinger-Ellison syndrome: pathogenesis, diagnosis and management. Am J Gastroenterol 1996;92(Suppl 4):445-85.
7. Ruuska T, Vaajalahti P, Arajarvi P, Maki M. Prospective evaluation of upper gastrointestinal mucosal lesions in children with ulcerative colitis and Crohn's disease. J Pediatr Gastroenterol Nutr 1994;19:181-6.
8. Rao S, Royal LE, Conrad HA, Harris V, Ahuja J. Duodenal ulcer in sickle cell disease. J Pediatr Gastroenterol Nutr 1990;10:117-20.
9. Laine L, Hopkins RJ, Girardi LS. Has the impact of *Helicobacter pylori* therapy on ulcer recurrence in the United States been overstated? A meta-analysis of rigorously designed trials. Am J Gastroenterol 1998;93:1409-15.
10. Bourke B, Jones N, Sherman P. *Helicobacter pylori* infection and peptic ulcer disease in children. Pediatr Infect Dis J 1996;15:1-13.
11. Gold BD. Pediatric *Helicobacter pylori* infection: clinical manifestations, diagnosis and therapy. In: Westblom TU, Czinn SJ, Nedrud JG, eds. Gastroduodenal Disease and *Helicobacter pylori*: Pathophysiology, Diagnosis and Treatment. Current Topics in Microbiology and Immunology. Berlin: Springer, 1999:71-102.
12. Nagita A, Amemoto K, Yoden A, et al. Diurnal variation in intragastric pH in children with and without peptic ulcers. Pediatr Res 1996;40:528-32.
13. Mertz-Nielsen AJH, Frokiare H, Bukhave K, Rask-Madsen J. Gastric bicarbonate secretion and release of prostaglandin E2 are increased in duodenal ulcer patients but not in *Helicobacter pylori* positive healthy subjects. Scand J Gastroenterol 1996;31:38-43.
14. Gold BD, Islur P, Policova Z, Czinn S, Neumann AW, Sherman PM. Surface properties of *Helicobacter mustelae* and ferret gastrointestinal mucosa. Clin Invest Med 1996;19:92-100.
15. Lichtenberger LM, Romero JJ. Effect of ammonium ion on the hydrophobic and barrier properties of the gastric mucus layer: implications on the role of ammonium in *H pylori* induced gastritis. J Gastroenterol Hepatol 1994;9:S13-9.
16. Warren JR, Marshall BJ. Unidentified curved bacilli on gastric epithelium in active chronic gastritis. Lancet 1983;i:1272-5.
17. Hill R, Pearman J, Worthy P, Caruso V, Goodwin S, Blincow E. *Campylobacter pyloridis* and gastritis in children. Lancet 1986;i:387.
18. Cadranel S, Goossens H, De Boeck M, Malengreau A, Rodesch P, Butzler JP. *Camplylobacter pyloridis* in children. Lancet 1986;i:735-6.
19. Drumm BPS, Cutz E, Karmali M. Association of *Campylobacter pylori* on the gastric mucosa with antral gastritis in children. N Engl J Med 1987;316:1557-61.
20. Czinn S, Dahms B, Jacobs G, Kaplan B, Rothstein F. Campylobacter-like organisms in association with symptomatic gastritis in children. J Pediatr 1986;109:80-3.
21. NIH Consensus Development Panel on *Helicobacter pylori* in Peptic Ulcer Disease. *Helicobacter pylori* in peptic ulcer disease. JAMA 1994;272:65-9.
22. The European *Helicobacter pylori* Study Group (EHPSG). Current European concepts in the management of *H pylori* infection: The Maastricht Consensus Report. Gut 1997;41:8-13.
23. Lee J, O'Morain C. Who should be treated for *Helicobacter pylori* infection? A review of Consensus Conferences and Guidelines. Gastroenterology 1997;113:S99-106.
24. Fennerty MB. What are treatment goals for *Helicobacter pylori* infection? Gastroenterology 1997;113:S120-6.
25. Hunt R, Thomson ABR. Canadian *Helicobacter pylori* Consensus Conference. Can J Gastroenterol 1998;12:31-41.
26. Lam SK, Talley NJ. *Helicobacter pylori* consensus: report of the 1997 Asia-Pacific consensus conference on the management of *Helicobacter pylori* infection. J Gastroenterol Hepatol 1998;13:1-12.
27. Luthra GK, DiNuzzo AR, Gourley WK, et al. Comparison of biopsy and serological methods of diagnosis of *Helicobacter pylori* infection and the potential role of antibiotics. Am J Gastroenterol 1998;93:1291-6.
28. Cutler AF, Havstad S, Ma CK, et al. Accuracy of invasive and noninvasive tests to diagnose *Helicobacter pylori* infection. Gastroenterology 1995;109:136-41.
29. Laine L, Lewin DN, Naritoku W, et al. Prospective comparison of H&E, Giemsa, and Genta stains for the diagnosis of *Helicobacter pylori*. Gastrointest Endosc 1997;45:463-7.
30. Satoh K , Kimura K, Taniguchi Y, et al. Biopsy sites suitable for the diagnosis of *Helicobacter pylori* infection and the assessment of the extent of atrophic gastritis. Am J Gastroenterol 1998;93:569-73.
31. Genta RM, Graham DY. Comparison of biopsy sites for the histopathologic diagnosis of *Helicobacter pylori*: A topographic study of *H pylori* density and distribution. Gastrointest Endosc 1994;40:342-5.
32. Bazzoli F, Zagari M, Fossi S, et al. Urea breath test for the detection of *Helicobacter pylori* infection. Helicobacter 1997;2:S34-7.
33. Rowland M, Lambert I, Gormally S, et al. Carbon 13-labeled urea breath test for the diagnosis of *Helicobacter pylori* infection in children. J Pediatr 1997;131:815-20.
34. Kalach N, Briet F, Raymond J, et al. The ^{13}Carbon urea breath test for the noninvasive detection of *Helicobacter pylori* in children: Comparison with culture and determination of minimum analysis requirements. J Pediatr Gastroenterol Nutr 1998;26:291-6.
35. Bode G, Rothenbacher D, Brenner H, et al. Variation in ^{13}C-urea breath test value by nationality in *Helicobacter pylori*-infected children. Scand J Gastroenterol 1998;33:468-72.
36. Cadranel S, Corvaglia L, Bontems P, et al. Detection of *Helicobacter pylori* infection in children with a standardized and simplified ^{13}C-urea breath test. J Pediatr Gastroenterol Nutr 1998;27:275-80.
37. Jones NL, Bourke B, Sherman PM. Breath testing for *Helicobacter pylori* infection in children: A breath of fresh air? J Pediatr 1997;131:791-3.
38. Khanna B, Cutler A, Israel NR, et al. Use caution with serologic testing for *Helicobacter pylori* infection in children. J Infect Dis 1998;178:460-5.
39. Elitsur Y, Neace C, Triest WE. Comparison between a rapid office-based and ELISA serologic test in screening for *H pylori* in children. Helicobacter 1997;2:180-4.
40. Czinn SJ. Serodiagnosis of *Helicobacter pylori* in pediatric patients. J Pediatr Gastroenterol Nutr 1999;28:132-4.
41. Goggin N, Rowland M, Imrie C, Walsh D, Clyne M, Drumm B. Effect of *Helicobacter pylori* eradication on the natural history of duodenal ulcer disease. Arch Dis Child 1998;79:502-5.
42. Rokkas T, Karameris A, Mavrogeorgis A, Rallis E, Giannikos N. Eradication of *Helicobacter pylori* reduces the possibility of rebleeding in peptic ulcer disease. Gastrointest Endosc 1995;41:1-4.
43. Jaspersen D, Koerner T, Schow W, Brennenstuhl M, Raschka C, Hammar C-H. *Helicobacter pylori* eradication reduces the rate of rebleeding in ulcer hemorrhage. Gastrointest Endosc 1995;41:5-7.
44. Roggero E, Zucca E, Pinotti G, et al. Eradication of *Helicobacter pylori* infection in primary low-grade astric lymphoma of mucosa-associated lymphoid tissue. Ann Intern Med 1995;122:767-9.
45. Bayerdorffer E, Newbauer A, Rudolph B, et al. Regression of primary gastric lymphoma of mucosa-associated lymphoid tissue after cure of *Helicobacter pylori* infection. Lancet 1995;345:1591-4.
46. Blecker U, McKeithan TW, Hart J, Kirschner BS. Resolution of *Helicobacter pylori*-associated gastric lymphoproliferative disease in a child. Gastroenterology 1995;109:973-7.
47. Talley NJ. A critique of therapeutic trials in *Helicobacter pylori* positive functional dyspepsia. Gastroenterology 1994;106:1174-83.
48. Gormally SM, Prakash N, Durnin MT, et al. Association of symptoms with *Helicobacter pylori* infection in children. J Pediatr 1995;126:753-6.
49. Graham DY, Lew GM, Malaty HM, et al. Factors influencing the eradication of *Helicobacter pylori* with triple therapy. Gastroenterology 1992;102:493-6.
50. Cutler A, Schubert T. Patient factors affecting *Helicobacter pylori* eradication with triple therapy. Am J Gastroenterol 1993;88:505-9.
51. Thijs J, van Zwet A, Moolenaar W, Wolfhagen M, ten Bokkel H. Triple therapy vs. amoxicillin plus omeprazole for treatment of *Helicobacter pylori* infection: a multicenter, prospective, randomized controlled study of efficacy and side effects. Am J Gastroenterol 1996;91:93-7.
52. Graham DY. Antibiotic resistance in *Helicobacter pylori*: implications for therapy. Gastroenterology 1998;115:1272-7.
53. Dore MP, Osato MS, Kwon DH, Graham DY, el-Zaatari FA. Demonstration of unexpected antibiotic resistance of genotypically identical *Helicobacter pylori* isolates. Clin Infect Dis 1998;27:84-9.
54. Skolnick JV. Antibiotic resistance in *Helicobacter pylori*. Clin Infect Dis 1998;27:90-2.
55. Rozynek E, Dzierzanowska D, Celinska-Cedro D, Jeljaszewicz J. Primary resistance to metronidazole and other antibiotics of *Helicobacter pylori*

isolated from children in Poland. Eur J Clin Microbial Infect Dis 1997;16:943-4.
56. Glupczynski Y, Labbe M, Burette A, Deltenre M, Avesani V, Bruck C. Treatment failure of ofloxacin in *Campylobacter pylori* infection. Lancet 1987;i:1096.
57. Blanco M, Pajares JM, Jimenez ML, Lopez-Brea M. Effect of acid inhibition on *Campylobacter pylori*. Scand J Gastroenterol Suppl 1998;142:107-9.
58. Humphreys H, Bourke S, Dooley C, et al. Effect of treatment on *Campylobacter pylori* in peptic disease: a randomised prospective trial. Gut 1988;29:279-83.
59. Dooley CP, McKenna D, Humphreys H, et al. Histological gastritis in duodenal ulcer: relationship to *Campylobacter pylori* and effect of ulcer therapy. Am J Gastroenterol 1988;83:278-82.
60. Hui WM, Lam SK, Chau PY, et al. Persistence of *Campylobacter pylori* despite healing of duodenal ulcer and improvement of accompanying duodenitis and gastritis. Dig Dis Sci 1987;32:1255-60.
61. Marshall BJ, Goodwin CS, Warren JR, et al. Prospective double-blind trial of duodenal ulcer relapse after eradication of *Campylobacter pylori*. Lancet 1988;ii:1437-42.
62. Solcia E, Villani L, Fiocca R, et al. Effects of eradication of *Helicobacter pylori* on gastritis in duodenal ulcer patients. Scand J Gastroenterol Suppl 1994;201:28-34.
63. Sherman P, Shames B, Loo V, Matlow A, Drumm B, Penner J. Omeprazole therapy for *Helicobacter pylori* infection. Scand J Gastroenterol 1992;27:1018-22.
64. Vigneri S, Termini R, Scialabba A, Pisciotta G, Di Mario F. Omeprazole therapy modifies the gastric localization of *Helicobacter pylori*. Am J Gastroenterol 1991;86:1276. (Lett)
65. Peura D. *Helicobacter pylori*: rational management options. Am J Med 1998;105:424-30.
66. Marshall BJ, Barrett LJ, Prakash C, McCallum RW, Guerrant RL. Urea protects *Helicobacter (Camplyobacter) pylori* from the bacterial effect of acid. Gastroenterology 1990;99:697-707.
67. Fleyou JF, Bahame P, Smith AC, Stockbrugger RE, Rode J, Price AB. Pernicious anemia and *Campylobacter*-like organisms: is the gastric antrum resistant to colonization? Gut 1989;30:60-4.
68. Rosioru C, Glassman MS, Berezin SH, Bostwick HE, Halata M, Schwarz SM. Treatment of *Helicobacter pylori*-associated gastroduodenal disease in children. Clinical evaluation of antisecretory vs. antibacterial therapy. Dig Dis Sci 1993;38:123-8.
69. Logan R, Gummett P, Schaufelberger H, et al. Eradication of *Helicobacter pylori* with clarithromycin and omeprazole. Gut 1994;35:323-6.
70. Bayerdörffer E, Simon T, Bästlein C, Ottenjann R, Kasper G. Bismuth/ofloxacin combination for duodenal ulcer. Lancet 1987;ii:1467-8. (Lett)
71. Graham DY, Klein PD, Opekun AR, et al. In vivo susceptibility of *Campylobacter pylori*. Am J Gastroenterol 1989;84:233-8.
72. Wilhelmsen I, Weberg R, Berstad K, Hausken T, Hundal O, Berstad A. *Helicobacter pylori* eradication with bismuth subcitrate, oxytetracyclines and metronidazole in patients with peptic ulcer disease. Hepatogastroenterology 1994;41:43-7.
73. Borody TJ, Brandl S, Andrews P, Ferch N, Jankiewicz E, Hyland L. Use of high efficacy, lower dose triple therapy to reduce side effects of eradicating *Helicobacter pylori*. Am J Gastroenterol 1994;89:33-8.
74. Graham DY, Lew GM, Ramirez FC, Genta RM, Klein PD, Malaty HM. Short report: a non-metronidazole triple therapy for eradication of *Helicobacter pylori* infection – tetracycline, amoxicillin, bismuth. Aliment Pharmacol Ther 1993;7:111-3.
75. Bazzoli F, Zagari RM, Fossi S, et al. Short-term, low dose triple therapy for eradication of *Helicobacter pylori*. Eur J Gastroenterol Hepatol 1994;6:773-7.
76. Moayyedi P, Axon ATR. Efficacy of a new one week triple therapy regime in eradicating *Helicobacter pylori*. Gut 1994;35(Suppl):S248. (Abst)
77. Labenz J, Stolte M, Rühl GH, Becker T, Tillenburg B, Sollböhmer M, Börsch G. One week low dose triple therapy for cure of *Helicobacter pylori*. Eur J Gastroenterol Hepatol 1994;7:9-11.
78. Lind T, Veldhuyzen van Zanten SJO, Unge P, et al. Eradication of *Helicobacter pylori* using one-week triple therapies combining omeprazole with two antimicrobials: The MACH I study. Helicobacter 1996;1:138-44.
79. Hopkins RJ, Girardi LJ, Turney EA. Relationship between *Helicobacter pylori* eradication and reduced duodenal and gastric ulcer recurrence: a review. Gastroenterology 1996;110:1244-52.
80. Axon ATR. *Helicobacter pylori* therapy: effect on peptic ulcer disease. J Gastroenterol Hepatol 1991;6:131-7.
81. Rauws EAJ, Tytgat GNJ. Cure of duodenal ulcer associated with eradication of *Helicobacter pylori*. Lancet 1990;335:1233-5.
82. Malfertheiner P. Compliance, adverse events and antibiotic resistance in *Helicobacter pylori* treatment. Scand J Gastroenterol Suppl 1993;196:34-7.
83. Tucci A, Corinaldesi R, Stanghellini V, et al. One-day therapy for treatment of *Helicobacter pylori* infection. Dig Dis Sci 1993;38:1670-3.
84. Hopkins RJ. Current FDA-approved treatments for *Helicobacter pylori* and the FDA approval process. Gastroenterology 1997;113:S126-30.
85. Dohil R, Israel DM, Hassall E. Effective 2-week therapy for *Helicobacter pylori* disease in children. Am J Gastroenterol 1996;92:244-7.
86. Casswall TH, Alfven G, Drapinski M, Bergstrom M, Dahlstrom KA. One-week treatment with omeprazole, clarithromycin, and metronidazole in children with *Helicobacter pylori* infection. J Pediatr Gastroenterol Nutr 1998;28:415-8.
87. van der Wouden EJ, van Zwet AA, Vosmaer GD, Oom JA, de Jong A, Kleibeuker JH. Rapid increase in the prevalence of metronidazole-resistant Helicobacter pylori in the Netherlands. Emerg Infect Dis 1997;3:385-9.