Current therapy for Helicobacter pylori infection in children and adolescents

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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

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pediatric hospitals in the United States, to determine the prevalence of peptic ulcer disease in hospitalized children (unpublished data).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 duodenal inflammation (p. ex., gastritis, ulcers duodénaux et gastriques) chez les enfants et les adultes. Quatre conférences consensuelles tenues dans le monde ont réuni des médecins, des chercheurs, des épidémiologistes 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 1ère conférence consensuelle canadienne sur l’infection à H. pylori chez l’enfant, tenue à Victoria, en Colombie britannique, en novembre 1998.

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 adolescents. Quatre conférences consensuelles tenues dans le monde ont réuni des médecins, des chercheurs, des épidémiologistes 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 1ère conférence consensuelle canadienne sur l’infection à H. pylori chez l’enfant, tenue à Victoria, en Colombie britannique, en novembre 1998.

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cent of those with ulcers had hemorrhage, and only 17% of these had documented \textit{H pylori} infection. In comparison, 27% of those with inflammation had hemorrhage, and 6% had proven \textit{H pylori} infection. Of the 268 ulcer cases, 92 (34%) were duodenal ulcers and 136 (51%) were gastric ulcers. Overall, \textit{H pylori} infection was diagnosed in 39% of those with duodenal ulcer and 15% of those with gastric ulcer. However, this number may be artifically low due to both the low levels of testing, and the poorly validated and inaccurate tests employed to diagnose \textit{H pylori} infection. Additionally, because the International Classification of Diseases code for \textit{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 \textit{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 \textit{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, \textit{H pylori}. However, recent reports suggest that there may be a subset of up to 20% of children with \textit{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 \textit{H pylori}.

The outcome of gastroduodenal disease after \textit{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 \textit{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 \textit{H pylori} on gastric acid secretion is controversial. In particular, the effect of \textit{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, \textit{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 \textit{H pylori}-infected adult patients with duodenal ulcers (13). Additional studies of gastric acid production and duodenal bicarbonate secretion in \textit{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 heliobacter 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.

**\textit{H pylori} AS A GASTRIC PATHOGEN IN CHILDREN: HISTORICAL LANDMARKS**

When discussing treatment guidelines for \textit{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 \textit{H pylori} (then \textit{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 \textit{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 (14C-labelled urea) or stable, nonradioactive isotope (13C) 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 13C-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

<table>
<thead>
<tr>
<th>Antibiotic resistance</th>
<th>No Antibiotic resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metronidazole</td>
<td>Colloidal bismuth subcitrate</td>
</tr>
<tr>
<td>Tinidazole</td>
<td>Bismuth subsalicylate</td>
</tr>
<tr>
<td>Erythromycin base</td>
<td>Tetracycline</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>Doxycycline</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>Furanolidone</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>Nitrofurantoin</td>
</tr>
<tr>
<td>Norfloxacin</td>
<td></td>
</tr>
<tr>
<td>Amoxicillin or ampicillin</td>
<td></td>
</tr>
</tbody>
</table>

TABLE 2
Primary resistance to nitroimidazole compounds

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

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.
	er 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 inf-
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, hematocrit) 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 pylori* 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**

*H2*-receptor antagonists: Blanco et al (57) treated 59 patients with *H pylori*-associated gastric or duodenal ulcers with *H2*-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-

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**TABLE 3**

<table>
<thead>
<tr>
<th>Country</th>
<th>Number of strains</th>
<th>Resistance (%)</th>
<th>Methodology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Europe</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>France</td>
<td>97</td>
<td>9</td>
<td>E test</td>
</tr>
<tr>
<td>Belgium</td>
<td>18</td>
<td>11</td>
<td>Agar dilution</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>68</td>
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</tr>
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<td>Switzerland</td>
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<td>0</td>
<td>Disc diffusion</td>
</tr>
<tr>
<td>Africa</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Burkina Faso</td>
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<td>14</td>
<td>E test</td>
</tr>
<tr>
<td>United States</td>
<td>37</td>
<td>11</td>
<td>Agar dilution</td>
</tr>
<tr>
<td>Australia</td>
<td>108</td>
<td>2</td>
<td>Disc diffusion</td>
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</table>

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**TABLE 4**

<table>
<thead>
<tr>
<th>State</th>
<th>Number of strains tested</th>
<th>Resistance (mean %)</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Georgia</td>
<td>15</td>
<td>5</td>
<td>Clarithromycin</td>
</tr>
<tr>
<td>Alabama</td>
<td>4</td>
<td>25</td>
<td>Metronidazole</td>
</tr>
<tr>
<td>Florida</td>
<td>12</td>
<td>25</td>
<td>Clarithromycin</td>
</tr>
<tr>
<td>South Carolina</td>
<td>3</td>
<td>33</td>
<td>Metronidazole</td>
</tr>
<tr>
<td>Ohio</td>
<td>10</td>
<td>10</td>
<td>Metronidazole</td>
</tr>
</tbody>
</table>
effective 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 negative¹¹C-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 metronidazole 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 antisulcyler 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 \textit{H pylori} infection, it is of no surprise that investigators have tried to eradicate \textit{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 \textit{H Pylori} INFECTION IN CHILDREN**

Four categories of eradication regimens have been used to treat \textit{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 \textit{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.

**CONCLUSIONS**

There is a need to develop a proven, efficacious treatment for \textit{H pylori} infection in children. If it is accepted that gastric colonization by \textit{H pylori} is associated with pediatric gastroduodenal disease, then eradication of the organism must be the intent of the practitioner caring for the \textit{H pylori}-infected child. Therefore, the desired outcome for individuals caring for these children should be to eradicate \textit{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 \textit{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 \textit{H pylori}. For all these reasons, an ideal treatment for \textit{H pylori} in children has yet to be determined. Current \textit{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 \textit{H pylori}-infected children are critically needed. Only in this manner can evidence-based practice guidelines for \textit{H pylori} infection in children be established.
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