

Canadian Helicobacter Study Group Consensus Conference: Update on the approach to *Helicobacter pylori* infection in children and adolescents – An evidence-based evaluation

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As an update to previously published recommendations for the management of *Helicobacter pylori* infection, an evidence-based appraisal of 14 topics was undertaken in a consensus conference sponsored by the Canadian Helicobacter Study Group. The goal was to update guidelines based on the best available evidence using an established and uniform methodology to address and formulate recommendations for each topic. The degree of consensus for each recommendation is also presented. The clinical issues addressed and recommendations made were: population-based screening for *H pylori* in asymptomatic children to prevent gastric cancer is not warranted; testing for *H pylori* in children should be considered if there is a family history of gastric cancer; the goal of diagnostic interventions should be to determine the cause of presenting gastrointestinal symptoms and not the presence of *H pylori* infection; recurrent abdominal pain of childhood is not an indication to test for *H pylori* infection; *H pylori* testing is not required in patients with newly diagnosed gastroesophageal reflux disease; *H pylori* testing may be considered before the use of long-term proton pump inhibitor therapy; testing for *H pylori* infection should be considered in children with refractory iron deficiency anemia when no other cause has been found; when investigation of pediatric patients with persistent or severe upper abdominal symptoms is indicated, upper endoscopy with biopsy is the investigation of choice; the ¹³C-urea breath test is currently the best noninvasive diagnostic test for *H pylori* infection in children; there is currently insufficient evidence to recommend stool antigen tests as acceptable diagnostic tools for *H pylori* infection; serological antibody tests are not recommended as diagnostic tools for *H pylori* infection in children; first-line therapy for *H pylori* infection in children is a twice-daily, triple-drug regimen comprised of a proton pump inhibitor plus two antibiotics (clarithromycin plus amoxicillin or metronidazole); the optimal treatment period for *H pylori* infection in children is 14 days; and *H pylori* culture and antibiotic sensitivity testing should be made available to monitor population antibiotic resistance and manage treatment failures.

Key Words: Children; Consensus; Guideline; *H pylori*; *Helicobacter*

Conférence consensuelle du Groupe d'étude canadien sur l'*Helicobacter pylori* : Mise à jour de l'approche à l'infection à *Helicobacter pylori* chez les enfants et les adolescents – Une évaluation probante

Afin de mettre à jour des recommandations pour la prise en charge de l'infection à *Helicobacter pylori*, une évaluation probante de 14 sujets a été entreprise dans le cadre d'une conférence consensuelle commanditée par le Groupe d'étude canadien sur l'*Helicobacter pylori*. On visait ainsi à mettre à jour les lignes directrices d'après les meilleures données probantes disponibles au moyen d'une méthodologie établie et uniforme et à formuler des recommandations pour chaque sujet. Le degré de consensus de chaque recommandation est également présenté. Les enjeux cliniques abordés et les recommandations proposées s'établissent comme suit : le dépistage en population générale du *H pylori* chez les enfants asymptomatiques afin de prévenir le cancer gastrique n'est pas justifié; le dépistage du *H pylori* chez les enfants devrait être envisagé en présence d'antécédents familiaux de cancer gastrique; l'objectif des interventions diagnostiques devraient viser à déterminer la cause des symptômes gastro-intestinaux et non la présence d'infection à *H pylori*; les douleurs abdominales récurrentes de l'enfance ne constituent pas une indication pour procéder au dépistage de l'infection à *H pylori*; le dépistage du *H pylori* n'est pas nécessaire pour les patients chez qui on vient de diagnostiquer un reflux gastro-œsophagien pathologique; le dépistage du *H pylori* peut être envisagé avant le début d'un traitement prolongé aux inhibiteurs de la pompe à protons; le dépistage de l'infection à *H pylori* devrait être envisagé chez les enfants atteints d'une anémie ferriprive réfractaire lorsque aucune autre cause n'est découverte; lorsqu'une exploration de patients pédiatriques présentant des symptômes persistants ou graves de l'abdomen haut est indiquée, une endoscopie haute accompagnée d'une biopsie est l'exploration de choix; le test respiratoire à l'urée ¹³C représente actuellement la meilleure épreuve de dépistage non effractive de l'infection à *H pylori* chez les enfants; on ne possède pas assez de données probantes pour recommander le dépistage d'antigènes dans les selles comme outil diagnostique acceptable de l'infection à *H pylori*; le dépistage sérologique des anticorps n'est pas recommandé comme outil diagnostique de l'infection à *H pylori* chez les enfants; le traitement de première intention de l'infection à *H pylori* pour les enfants est une trithérapie biquotidienne composée d'un inhibiteur de la pompe à protons et de deux antibiotiques (clarithromycine et amoxicilline ou métronidazole); la période de traitement optimale de l'infection à *H pylori* est de 14 jours pour les enfants; une culture du *H pylori* et un test de sensibilité aux antibiotiques devraient être rendus disponibles pour surveiller l'antibiorésistance de la population et prendre en charge les échecs de traitement.

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Helicobacter pylori is an important global pathogen infecting approximately 50% of the world's population (1). In Canada, *H pylori* is thought to infect no more than 30% of the general population, but higher rates are found in some immigrant populations, Aboriginal people and the Inuit (2). Infected persons are at increased risk for the development of peptic ulcer disease (PUD), gastric adenocarcinoma and mucosa-associated lymphoid tissue lymphoma (1).

H pylori infection is usually acquired in childhood (3); however, children rarely develop severe complications. Therefore, guidelines governing the testing for, and treatment of, *H pylori* in the pediatric setting are clearly relevant. In 1999, the Canadian Helicobacter Study Group (CHSG) issued the first evidence-based collaborative recommendations aimed at defining appropriate management strategies for the identification and eradication of *H pylori* in children and adolescents (3). Additional pediatric guidelines for the management of *H pylori* have been generated in North America (4), Europe (5) and Japan (6).

Similar to the first consensus conference of the CHSG held in 1997 (7), attendees came from a wide range of backgrounds, including pediatric and adult gastroenterologists, pediatricians, basic scientists, microbiologists and primary care physicians. The purpose of the 2004 CHSG consensus conference was to revisit the peer-reviewed literature on *H pylori* infection in pediatrics, and to either reaffirm existing recommendations or to develop new ones based on the best available evidence. A total of 14 statements covering issues related to screening, testing and treatment of *H pylori* in children were discussed. For each of the statements, relevant data were presented and, subsequently, appraised and ranked by attendees. On a number of occasions, discussions arising from each of the statements resulted in a rewording of the originally proposed recommendation. All statements were voted on and ranked according to the quality and classification of currently available evidence.

IMPORTANT NEW INSIGHTS

As a prelude to the development of the 2004 CHSG consensus conference recommendations, members were updated with formal presentations on new insights regarding *H pylori* disease pathogenesis. These advances in the field are reviewed in detail in the papers accompanying the consensus document in the present issue of the *Journal*.

The overwhelming majority of *H pylori*-infected patients develop gastritis, but few develop complications associated with infection. It is estimated that the lifetime risk of an *H pylori*-infected patient developing PUD is approximately 10% to 15%, while less than 1% will develop gastric cancer (8). Current evidence indicates that disparate disease outcomes are not related solely to the genetic diversity of *H pylori*, but also to host factors and environmental agents (1). Further delineation of host response to infection, specific environmental exposures and bacterial virulence factors is required to identify which patients infected with *H pylori* are at greatest risk for developing clinical disease. Identifying and understanding such interactions should promote the development of novel diagnostic modalities and therapeutic interventions to optimize clinical outcomes.

CONSENSUS CONFERENCE STRUCTURE

As with past CHSG consensus conferences, broad interest groups were represented with expertise in a number of disciplines.

Included at this conference were representatives from pediatric and adult gastroenterology, infectious diseases, medical microbiology, primary care medicine, pharmacology, epidemiology and the basic sciences (microbiology, immunology and physiology). The consensus conference was sponsored by the CHSG, the Canadian Association of Gastroenterology, the Canadian Digestive Health Foundation, CanGut, the Association of Medical Microbiology and Infectious Diseases Canada and the Canadian Pediatric Society.

Financial support for the conference was provided through equal unrestricted educational grants from Altana Pharma Inc/Solvay Pharma Inc, AstraZeneca Canada Inc, Axcan Pharma Inc and Janssen-Ortho Inc. Representatives from the pharmaceutical industry were invited to attend but did not vote on the consensus recommendations.

CONSENSUS CONFERENCE PROCESSES

Each topic chosen for formulation of clinical recommendations was critically and independently evaluated. An overview of each issue based on comprehensive literature searches was presented by experts in the field. This was followed by a period of discussion, in which the existing data were evaluated and critiqued. At the end of the discussion, a recommendation with specific wording was formulated. Once an acceptable recommendation was established, formal voting was undertaken in three categories using a graded scale. In order, these were the quality of the evidence (Table 1); the classification of the evidence relative to the recommendation being made (Table 2); and the recommendation itself (Table 3). In the present paper, this order has been altered to place the vote on the recommendation first, followed by the voting on the quality of evidence and its classification.

Each section in the present report starts with the consensus recommendation. Thus, readers of the document can quickly familiarize themselves with the major conclusions. However, the relevance of these recommendations to individual patient care is best interpreted by also reviewing the quality of data on which the recommendations are based, the degree of consensus among the participating experts, and the reservations and issues of contention contained in the discussion sections. Unanimous votes were uncommon. However, it is important to emphasize that the basic premise of each recommendation was accepted by the majority.

Recommendation 1: Population screening for *H pylori* in asymptomatic children to prevent gastric cancer is not warranted

- Summary of the vote on the recommendation (Table 3)
A 50%, B 43%, C 7%, D 0%, E 0%
- Summary of the vote on the classification of the evidence (Table 2)
A 21%, B 61%, C 16%, D 2%, E 0%
- Summary of the vote on the quality of the evidence (Table 1)
A 21%, B 35%, C 32%, D 0%, E 12%

TABLE 1
Quality of evidence

A	I	At least one appropriately designed randomized controlled trial
B	II-1	At least one appropriately designed controlled trial without randomization
C	II-2	Cohort or case-controlled studies, preferably from one or more research groups
D	II-3	Substantial or marked results from uncontrolled studies
E	III	Opinions of experts based on clinical experience or descriptive studies

Recommendation 2: Testing for *H pylori* in children should be considered if there is a family history of gastric cancer

- Summary of the vote on the recommendation (Table 3)
A 51%, B 46%, C 3%, D 0%, E 0%
- Summary of the vote on the classification of the evidence (Table 2)
A 8%, B 56%, C 36%, D 0%, E 0%
- Summary of the vote on the quality of the evidence (Table 1)
A 11%, B 35%, C 40%, D 0%, E 14%

Discussion of recommendations 1 and 2

H pylori was first classified as a carcinogen by the World Health Organization in 1994 (9). Epidemiological data (10) support the role of *H pylori* in gastric carcinogenesis, with up to a four-fold OR for developing gastric cancer in an *H pylori*-infected individual. In a study of 1526 Japanese subjects by Uemura et al (11), 2.9% of *H pylori*-positive patients developed gastric cancer over a 7.8-year follow-up. In contrast, gastric cancer did not develop in *H pylori*-negative subjects. Koch's postulates have also been fulfilled for *H pylori* as a gastric carcinogen in an animal model of infection (12).

An important area of concern is whether *H pylori* infection is a modifiable risk factor for the development of gastric cancer. In a study (13) of high-risk adults, no reduction in gastric cancer risk at the end of 7.5 years of follow-up was observed in *H pylori* carriers who had previously undergone eradication therapy. However, in a subgroup analysis of patients who had no precancerous lesions at baseline, cancer risk was significantly reduced (13). Additional studies (14,15) suggest that prevention of gastric cancer may be possible in infected individuals without precancerous lesions. Current evidence indicates that children rarely exhibit the precancerous lesions of gastric atrophy or intestinal metaplasia (16-18). Therefore, they may well be the group to target in an effort to prevent the future development of gastric cancer.

Cost-benefit analysis indicates that in areas with a low prevalence of *H pylori* infection, a test-and-treat strategy in children is not economically feasible, with costs of US\$869,000 per year of life saved (19). According to a recent epidemiological survey (20), the seroprevalence of *H pylori* infection in American children between six and 19 years of age has dropped dramatically across multiple ethnic groups. However, *H pylori* seroprevalence remains relatively high, at approximately 35% among foreign-born United States residents. Similar prevalence

TABLE 2
Classification of evidence

A	Good supportive evidence
B	Fair supportive evidence
C	Poor supportive evidence, but recommendations reasonable on other grounds
D	Fair contrary evidence
E	Good contrary evidence

TABLE 3
Voting on recommendations

A	Accept completely
B	Accept with some reservation
C	Accept with major reservation
D	Reject with reservation
E	Reject completely

figures have been reported for Canadian adults with dyspepsia (21). In an unpublished study of 246 Canadian children aged five to 18 years seen in outpatient gastroenterology clinics because of upper gastrointestinal (GI) tract symptoms who subsequently underwent endoscopy and biopsy, the prevalence of *H pylori* infection was 5.3%. However, Aboriginals and immigrants to Canada are at much higher risk for *H pylori* infection. For example, in one report (2), over 90% of First Nations persons were *H pylori*-seropositive by 15 years of age (2). In a study from British Columbia (22), of those children who were found to have *H pylori*-associated PUD at endoscopy, the great majority were Aboriginal or immigrant, while those with non-*H pylori* PUD were largely Caucasian (22). Thus, the prevalence of *H pylori* among Canadian children is variable and is largely related to immigrant or Aboriginal status.

Given the overall low prevalence of *H pylori* infection in Canadian children, a population-wide screen-and-treat strategy is not warranted and is likely not economically feasible. However, initiation of screening in children in high-risk populations might well prove to be cost-effective. Based on the available evidence, it was recommended that physicians choose to test and treat *H pylori* infection on an individual basis, and consider testing and treating children whose country of origin has a high risk of gastric cancer (eg, Japan). CHSG participants also thought it was reasonable to test for and treat *H pylori* infection in children if parents are concerned about gastric cancer because of a family history.

Perhaps most important, to reduce *H pylori* infection rates and, thereby, lower the risk for developing PUD later in life, CHSG members made a strong plea for better public health conditions for Aboriginals.

Recommendation 3: The goal of diagnostic interventions should be to determine the cause of presenting GI symptoms, and not the presence of *H pylori* infection

- Summary of the vote on the recommendation (Table 3)
A 68%, B 26%, C 3%, D 3%, E 0%
- Summary of the vote on the classification of the evidence (Table 2)
A 20%, B 43%, C 34%, D 0%, E 3%

- Summary of the vote on the quality of evidence (Table 1)
A 17%, B 17%, C 28%, D 21%, E 17%

Recommendation 4: Recurrent abdominal pain is not an indication to test for *H pylori* infection

- Summary of the vote on the recommendation (Table 3)
A 72%, B 25%, C 3%, D 0%, E 0%
- Summary of the vote on the classification of the evidence (Table 2)
A 47%, B 39%, C 14%, D 0%, E 0%
- Summary of the vote on the quality of the evidence (Table 1)
A 40%, B 26%, C 23%, D 3 %, E 8%

Discussion of recommendations 3 and 4

Discussion focused on whether children with recurrent abdominal pain (RAP) or functional dyspepsia should be screened for *H pylori* infection. For the purposes of discussion, RAP was defined as any child or adolescent who has recurrent episodes of abdominal pain (as defined by Apley and Naish [23] – at least three discrete episodes of abdominal pain over a three-month period of sufficient severity to disrupt normal activities) for which the family seeks medical attention and an explanation (24). Published studies have described associations of RAP in *H pylori*-infected children compared with those without; have had a variety of diagnostic methods used to detect *H pylori* cases; or described *H pylori* eradication in children with RAP to determine cause and effect (3-5). There is a paucity of randomized placebo-controlled trials with well-defined *H pylori*-infected cases and a validated symptom assessment instrument used at baseline and end point.

RAP is common in childhood, occurring in up to 35% of children between five and 15 years of age (24). Although RAP often leads to extensive diagnostic investigation, over 90% of children with RAP will have no identifiable organic cause and are given a 'functional' explanation for their symptoms. Because *H pylori* induces gastritis, it is feasible that gastric inflammation may cause clinically reportable symptoms. Therefore, the potential role of *H pylori* causing RAP has been the focus of much research.

In a systematic review, Macarthur et al (25) found no temporal relationship, no biological plausibility and no supporting experimental evidence for a role of *H pylori* infection in RAP in childhood. Case control trials (26) identify a similar prevalence of *H pylori* infection in children with and without functional abdominal pain. Results from six separate studies (27-32) carried out in North America, Europe and Australia, involving over 2700 children, indicate that between 5% and 17% of children with abdominal pain have *H pylori* infection, while a comparable frequency (5% to 29%) of children without abdominal pain also have the infection (27-32).

Investigators have not yet identified any significant pattern of symptoms that segregates children with *H pylori* infection from uninfected age-matched community controls (reviewed by Sherman and Macarthur [33]). Furthermore, in a recent randomized controlled trial (34) in which 20 children with RAP or dyspepsia (defined as "nonspecific symptoms related to the upper GI tract") received either anti-*Helicobacter* treatment

or proton pump inhibitors (PPIs) with placebo, eradication of *H pylori* infection did not result in an improvement in clinical symptoms. Taken together, it was thought that evidence supporting a causal relationship between *H pylori* infection and symptoms of RAP was at best inconsistent. Therefore, current data indicate that the goal of diagnostic interventions should be to detect the underlying pathophysiology and cause of clinical symptoms, not simply the presence of *H pylori*. It was agreed that more research is needed in this area to identify subsets of children who may benefit from testing for the presence of *H pylori* and subsequent eradication of the organism.

Recommendation 5: *H pylori* testing is not required in patients with newly diagnosed gastroesophageal reflux disease

- Summary of the vote on the recommendation (Table 3)
A 71%, B 29%, C 0%, D 0%, E 0%
- Summary of the vote on the classification of the evidence (Table 2)
A 42%, B 31%, C 19%, D 18%, E 0%
- Summary of vote on the quality of the evidence (Table 1)
A 75%, B 14%, C 8%, D 3%, E 0%

Recommendation 6: *H pylori* testing may be considered before long-term PPI therapy

- Summary of the vote on the recommendation (Table 3)
A 49%, B 45%, C 3%, D 3%, E 0%
- Summary of the vote on the classification of the evidence (Table 2)
A 11%, B 64%, C 22%, D 3%, E 0%
- Summary of the vote on the quality of the evidence (Table 1)
A 42%, B 33%, C 8%, D 6 %, E 11%

Discussion of recommendations 5 and 6

The prevalence of gastroesophageal reflux disease (GERD) increases with age, from 2.5% of children between the ages of three and nine years to 8.5% in children between the ages of 10 and 17 years (35). Whether *H pylori* infection contributes to the development of GERD – and whether its eradication favourably influences the natural history of GERD – was debated by the group. Conflicting results exist in the limited studies investigating the role of *H pylori* in GERD in children (36-39). In addition, studies suffer from design limitations and differing outcome measures. The limitation in making an evidence-based decision is the paucity of well-designed, prospective randomized controlled trials in children with relevant upper GI tract symptoms and/or objective clinical markers of disease.

There are several large randomized controlled trials in adults with GERD. For example, in one randomized trial (40), *H pylori* eradication did not alter the relapse rate of GERD-related symptoms. In another, *H pylori* eradication did not influence reflux symptoms (41).

Taken together, the evidence that *H pylori* eradication influences the course of GERD – in children or adults – is not

compelling. Therefore, it was concluded that *H pylori* testing is not required in patients with newly diagnosed GERD.

An area of contention was the association between *H pylori* infection, long-term PPI therapy for GERD and worsening of histological gastritis. The question of whether *H pylori* increases the susceptibility to develop gastric cancer during chronic PPI therapy was debated. This concern was initially fuelled by a study in adults (42) suggesting that *H pylori* infection exacerbates atrophic gastritis with concurrent chronic PPI therapy. However, the study methodology has since been criticized.

Subsequent studies (43) provide conflicting results regarding whether there is an acceleration of gastric atrophy in *H pylori*-infected subjects on PPI as maintenance therapy for GERD. Current evidence indicates that PPI use does alter the distribution of *H pylori*-induced gastritis, promoting a body-predominant form (44,45). A randomized controlled trial (46) identified a reduction in corpus gastritis following *H pylori* eradication in adults on PPI maintenance therapy. However, it remains unknown whether the PPI-induced change in the pattern of gastritis increases the risk for the later development of gastric cancer. Therefore, it remains uncertain whether *H pylori* eradication will result in any benefit (ie, have an effect on reduction of overall gastric cancer risk). Despite the absence of data indicating a proven clinical benefit from testing and treating for *H pylori* infection before the initiation of long-term PPI therapy, the theoretical benefit of improving body gastritis and eliminating the risk of *H pylori*-related diseases prompted a small majority of CHSG participants to support this recommendation.

Recommendation 7: Testing for *H pylori* infection should be considered in children with refractory iron deficiency anemia when no other cause has been found

- Summary of the vote on the recommendation (Table 3)
A 67%, B 30%, C 3%, D 0%, E 0%
- Summary of the vote on the classification of the evidence (Table 2)
A 20%, B 63%, C 17%, D 0%, E 0%
- Summary of the vote on the quality of the evidence (Table 1)
A 17%, B 34%, C 37%, D 6%, E 6%

Discussion of recommendation 7

The revised consensus document on the management of *H pylori* in children was expanded to include extraintestinal diseases in which *H pylori* infection may play a causative role. Due to the worldwide prevalence of this infection, epidemiological associations with a number of human diseases have been described. In particular, *H pylori* has been implicated in a wide range of extraintestinal conditions, including short stature, immune thrombocytopenic purpura (ITP) and refractory iron deficiency anemia (33). Evidence supporting a causal role for *H pylori* for most of these diseases is, at best, weak.

In some studies, short stature has been linked to *H pylori* infection in children, but almost an equal number of publications report no impact of *H pylori* infection on growth (33,47-49). In patients with ITP, some authors (50,51) report an increase in platelet counts following *H pylori* eradication; however, these studies typically lack control groups and only small

numbers of ITP patients were treated for *H pylori*, making any population-based extrapolations tenuous.

In contrast, accumulating evidence supports an association between *H pylori* infection and unexplained refractory iron deficiency anemia. In case controlled studies (52), both in adults and children, reduced ferritin and iron levels are identified in *H pylori*-infected subjects. In one study (53) of adolescent females with iron deficiency anemia, eradication of *H pylori* improved hemoglobin concentration and serum iron and ferritin levels. In contrast, these parameters did not change significantly following oral iron therapy alone. There is also biological plausibility for this association (33); although *H pylori* infection can induce GI blood loss, most studies have not documented occult bleeding in iron deficient subjects. Instead, it is thought that decreased iron absorption is due to either reduced gastric ascorbic acid concentrations or to the potential iron scavenging mechanisms that *H pylori* possesses (54,55).

Based on this emerging evidence, the presence of iron deficiency anemia in an individual (in whom other causes such as celiac disease have been excluded) was considered an indication to test and treat for *H pylori* infection.

Recommendation 8: When investigation of children with persistent or severe upper abdominal symptoms is indicated, GI endoscopy with biopsy is the investigation of choice

- Summary of the vote on the recommendation (Table 3)
A 71%, B 26%, C 3%, D 0%, E 0%
- Summary of vote on the classification of the evidence (Table 2)
A 33%, B 35%, C 32%, D 0%, E 0%
- Summary of the vote on the quality of evidence (Table 1)
A 12%, B 21%, C 26%, D 18%, E 23%

Discussion of recommendation 8

The current gold standard for the detection of *H pylori* in children remains upper endoscopy plus mucosal biopsies (3-5). Endoscopy has the added advantage of being able to detect complications of *H pylori* infection, and to rule out other upper GI pathologies. An additional advantage of endoscopy and biopsy is that it allows physicians to obtain gastric mucosa for urease testing, histological examination and bacterial culture to subsequently determine antibiotic resistance. However, endoscopy is also expensive and, in children, requires the use of conscious sedation or anesthesia. Endoscopy also carries a small risk of perforation and aspiration pneumonia.

In children, there is a fairly high correlation between the presence of antral nodularity on endoscopy and the presence of *H pylori* infection, particularly when PUD is present (22,56). Regardless of endoscopic findings, it is essential to biopsy the antrum, where several studies indicate the yield for *H pylori* is the highest (57). However, a recent study (58) in Italian children investigating the potential causes of carditis found a high yield for detection of *H pylori* in biopsies obtained from the gastric cardia. Studies performed in adults (59) suggest that during PPI therapy, the yield for identifying *H pylori* is enhanced by also obtaining a biopsy from the corpus. Thus, in children on PPI therapy, biopsies from the corpus may enhance detection of *H pylori* infection. Among the various histological

stains used to identify the organism, results are comparable (60) even though there are considerable differences in their cost.

The 'string' test, where a piece of string is encapsulated in gelatin and swallowed, soaking up gastric contents, is not as sensitive as biopsy, although it is equally specific (61). Most polymerase chain reaction-based detection methods for *H pylori* are not as accurate as histology or urease testing (62).

Taken together, the collective evidence indicates that, at present, endoscopy is the best invasive test for the detection of *H pylori* infection and its complications. However, the main goal of endoscopy is as a tool to investigate the cause of the patient's complaints and not solely to look for *H pylori* infection.

Recommendation 9: The ^{13}C -urea breath test is the best noninvasive diagnostic test for *H pylori* infection in children

- Summary of the vote on the recommendation (Table 3)
A 72%, B 25%, C 3%, D 0%, E 0%
- Summary of the vote on classification of the evidence (Table 2)
A 70%, B 30%, C 0%, D 0%, E 0%
- Summary of the vote on the quality of evidence (Table 1)
A 85%, B 15%, C 0%, D 0%, E 0%

Discussion of recommendation 9

A number of noninvasive diagnostic tests are now available for the detection of *H pylori* infection (63), none of which are 100% sensitive and specific. Urea breath tests (UBTs) are noninvasive and detect the presence of urease-producing organisms such as *H pylori* in the stomach (64). Many researchers have attempted to identify the optimal test conditions for the ^{13}C -UBT in children (65,66). An acid environment in the stomach is optimal, but not necessarily required to identify *H pylori* with the ^{13}C -UBT in children (67). Changes over baseline values in ^{13}C -UBT are also higher when the test is performed in a fasting state (ie, at least 4 h after a meal), compared with 1 h to 2 h postprandially (66). A 200 mL citric acid solution (20 mg/mL) as a test meal is also superior to Ensure pudding (Abbot Laboratories, USA), provided that the child's mouth is rinsed after intake of tracer (67,68).

To date, studies indicate that the ^{13}C -UBT test is reliable for detecting the presence of *H pylori* in children older than six years of age, regardless of the precise test conditions (4,65). However, there are more false-positive results (approximately 8%) in children younger than six years of age (66,69,70), particularly in infants (71). Recent evidence (68) suggests that the ^{13}C -UBT still may be used in young children, but the specificity can be improved by giving a lower tracer dose (68) and adjusting for CO_2 production rates (72). Rinsing the mouth after intake of the tracer can avoid false-positive results by urease-producing oral bacterial flora (71).

Antibiotic monotherapy for other infections can cause false-negative test results (73). Similarly, PPI therapy may also result in false negatives (74). Based on data in adults, it is recommended that antibiotics should be stopped for at least four weeks before ^{13}C -UBT, and that PPIs should be stopped for at least two weeks before testing (75).

In summary, the ^{13}C -UBT is currently considered to be the best available noninvasive diagnostic test for detection of *H pylori* infection in children.

Recommendation 10: There is currently insufficient evidence to recommend stool antigen tests as an acceptable noninvasive diagnostic tool for *H pylori* in children

- Summary of the vote on the recommendation (Table 3)
A 45%, B 42%, C 8%, D 5%, E 0%
- Summary of the vote for the classification of the evidence (Table 2)
A 14%, B 75%, C 8%, D 3%, E 0%
- Summary of the vote on the quality of the evidence (Table 1)
A 32%, B 52%, C 13%, D 3%, E 0%

Discussion of recommendation 10

Several different *H pylori* stool antigen tests are now available commercially. These include assays based on either polyclonal or monoclonal antibodies. The polyclonal antibody-based test is not as reliable as the UBT for detecting *H pylori*, either for initial diagnosis or following *H pylori* eradication therapy (68,76-79). However, a monoclonal antibody-based test does appear to be as reliable as the UBT in both the pre- and post-treatment settings, showing excellent separation between true-positive and true-negative results (80). An advantage of the *H pylori* stool test is that it is easy to perform, and the results appear to be independent of age (76). Furthermore, they are also less costly than the UBT. However, studies to date using stool antigen tests in North American children are limited and have been carried out primarily in specialized referral centres; therefore, results may well differ when the tests are evaluated and analyzed in a nonspecialized laboratory in a community practice setting. In addition, further validation is required in specific populations, including areas of low *H pylori* prevalence, such as most of Canada.

In summary, initial results indicate that the monoclonal antibody stool antigen test performs as well as the UBT in a variety of settings. However, given the lack of evidence supporting its accuracy outside of controlled studies and in different populations, it was judged to be too premature to recommend stool antigen testing as an alternative to UBT at the present time.

Recommendation 11: Serological antibody tests are not recommended as diagnostic tools for *H pylori* in children

- Summary of the vote on the recommendation (Table 3)
A 64%, B 38%, C 5%, D 3%, E 0%
- Summary of the vote on the classification of recommendation (Table 2)
A 49%, B 37%, C 11%, D 3%, E 0%
- Summary of the vote on the quality of evidence (Table 1)
A 56%, B 33%, C 8%, D 3%, E 0%

Discussion of recommendation 11

Despite a low accuracy in young children (81), and the recommendations from Canadian, North American and European

clinical practice guidelines that serological-based assays to detect *H pylori* should not be used, serum antibody tests continue to be widely used in Canada. Some commercial *H pylori* serological tests have a sensitivity of less than 50% in children between the ages of two and six years (81,82). In addition, different commercial tests may give very diverse results when applied on the same sera (82). Finally, *H pylori*-positive serology does not distinguish between active or past infection.

Despite a potentially high negative predictive value, the positive predictive value of serological assays is low (81,83). The use of serology to detect *H pylori* infection could give false-positive test results in a large proportion of infected children under the age of six years (83,84). It has been suggested by some that the low accuracy of these tests does not justify their use on clinical or economical grounds in both children and adults (63). Because the goal of diagnostic interventions is to identify the cause of presenting GI symptoms, and not the presence of *H pylori* infection (see recommendation 3), the use of serology-based assays cannot be advocated.

Recommendation 12: First-line therapy for *H pylori* infection is a twice-daily, triple-drug regimen comprised of a PPI plus two antibiotics (clarithromycin plus amoxicillin or metronidazole)

- Summary of the vote on the recommendation (Table 3)
A 63%, B 32%, C 5%, D 0%, E 0%
- Summary of the vote on the classification of the evidence (Table 2)
A 59%, B 38%, C 3%, D 0%, E 0%
- Summary of the vote on the quality of the evidence (Table 1)
A 54%, B 43%, C 3%, D 0%, E 0%

Recommendation 13: Optimal treatment duration is 14 days

- Summary of the vote on the recommendation (Table 3)
A 54%, B 43%, C 3%, D 0%, E 0%
- Summary of the vote on the classification of the evidence (Table 2)
A 59%, B 38%, C 3%, D 0%, E 0%
- Summary of the vote on the quality of the evidence (Table 1)
A 54%, B 43%, C 3%, D 0%, E 0%

Discussion of recommendations 12 and 13

The results of 72 studies of *H pylori* treatment in children were reviewed in a recent meta-analysis (unpublished data). Over two-thirds of the studies were peer-reviewed, but only 9% were randomized controlled studies, and only one was a randomized placebo-controlled study. The meta-analysis showed that the proportion of *H pylori* infections successfully eradicated with either single or dual-agent regimens is low. With triple therapies, after one to two weeks of treatment, eradication rates ranged from a low of 65% to over 90% (unpublished data). One multicentre prospective randomized double-blind controlled pediatric trial compared the efficacy of triple therapy (consisting of omeprazole, amoxicillin and clarithromycin for

one week) with dual therapy (amoxicillin and clarithromycin) (85). In the intent-to-treat analysis, the eradication rate was 74.2% with triple therapy compared with only 9.4% with dual therapy ($P < 0.01$). However, the success rate with triple therapy is below the recommended 80% cure rate by intent-to-treat analysis for acceptable treatment in adults (6).

Recommended first-line therapy for use in *H pylori* eradication in adults consisted of a PPI, clarithromycin, and amoxicillin or metronidazole, given for seven to 10 days. Alternatively, a PPI can be combined with bismuth, tetracycline and metronidazole, given for 10 to 14 days (7). A number of new approaches have been tested as an initial therapy for adult patients, including quinolone-based triple therapy. Results from a few randomized studies (86-88) indicate that quinolone-based triple regimens achieve acceptable eradication rates when used as first-line therapy, but the data for treatment failures are conflicting. There are no data on the use of quinolone-based therapies in *H pylori*-infected children.

Based on these data, it was agreed that the recommended first-line eradication therapy should include a PPI and clarithromycin, in combination with either metronidazole or amoxicillin, for a period of 14 days. Metronidazole has an unpleasant taste, which can compromise compliance. Because clarithromycin and amoxicillin are both available in liquid formulations, they are easier to use in children. Tetracycline should be avoided in children younger than 12 years of age because it may cause abnormalities in dentition.

There was considerable debate regarding the optimal treatment period. Published literature is supportive, but not conclusive, of an optimal treatment duration of 14 days. A meta-analysis (89) involving 13 studies in adults, in which either a PPI-clarithromycin/amoxicillin regimen or a PPI-clarithromycin/metronidazole regimen were given for seven, 10 or 14 days indicated that a 14-day regimen produced between 7% and 9% higher eradication rates compared with seven-day treatment regimens. In contrast, Oderda et al (90) systematically reviewed treatment trials in children and found that the duration of therapy did not appear to affect eradication rates, at least when using a PPI-based triple therapy regimen.

Because emergence of resistance to antibiotics following treatment failure is an area of concern (91), the best available first-line therapy should be employed. Therefore, it was agreed that, although not conclusive, the available literature supports the concept that higher eradication rates may be achieved by using a longer duration of triple therapy (ie, 14 days).

Recommendation 14: *H pylori* culture and antibiotic sensitivity testing should be available to monitor population antibiotic resistance and to manage treatment failures

- Summary of the vote on the recommendation (Table 3)
A 73%, B 21%, C 3%, D 3%, E 0%
- Summary of the vote on the classification of the evidence (Table 2)
A 11%, B 35%, C 51%, D 3%, E 0%
- Summary of the vote on the quality of the evidence (Table 1)
A 9%, B 11%, C 9%, D 9%, E 62%

Discussion of recommendation 14

Current evidence from studies (92) in adults indicates that antibiotic resistance adversely affects therapeutic efficacy. The prevalence of primary antibiotic resistance varies in different countries and is evolving over time. In Canada, metronidazole resistance appears to be stable at approximately 20% (91). Resistance to clarithromycin is increasing in Canada, but is still low relative to many other countries at approximately 8% (91). Amoxicillin resistance is minimal.

Limited data with respect to population-based antibiotic sensitivity exist in Canadian children. In Europe, the reported prevalence of clarithromycin resistance in children ranges from 12% to 20% (92). Clarithromycin resistance in *H pylori* cultured from children in the United States is approximately 13% (94). Primary metronidazole resistance ranges from 15% to 43% in European children (92). In the United States, resistance to metronidazole is approximately 25% (92). Primary resistance to amoxicillin has only rarely been reported (92,93).

Based on concerns surrounding antibiotic resistance, CHSG members recommended that reference laboratories be

available to culture *H pylori* and perform antibiotic sensitivity testing to monitor population antibiotic resistance and aid in the management of treatment failures.

CONCLUSIONS

The prevalence of *H pylori* infection in Canada is changing and the clinical implications of infection in childhood continue to evolve. The goal of the recommendations made by the CHSG is to provide updated management strategies reflecting evolving knowledge to improve patient care. In addition, it is intended that the updated guidelines will continue to persuade health care administrators to facilitate and implement new recommendations. Moreover, the CHSG strongly supported ongoing clinical and basic research required to advance knowledge and, thereby, improve the overall care of *H pylori*-infected children. Finally, the CHSG made a strong plea for continued improvement in the social circumstances of children, not only with respect to the potential for reducing *H pylori* infection, but also to promote enhanced child health and well-being in general.

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ERRATUM

NL Jones, P Sherman, CA Fallone, et al; for the Canadian Helicobacter Study Group. Canadian Helicobacter Study Group Consensus Conference: Update on the approach to *Helicobacter pylori* infection in children and adolescents – An evidence-based evaluation. Can J Gastroenterol 2005;19(7):399-408.

The names of a number of authors were inadvertently omitted from the above publication, and are listed below in their entirety. Pulsus Group Inc would like to extend their apologies in this matter.

Participants in the Canadian Helicobacter Consensus Conference on Pediatric Issues: The following individuals provided a presentation of the best available evidence for each of the given topics and are co-authors: Billy Bourke, Peter Ceponis, Naoki Chiba, Steve Czinn, Richard Ferraro, Lori Fischbach, Ben Gold, Hien Hyunh, Kevan Jacobson, Nicola Jones, Sibylle Koletzko, Sylvie Lebel, Paul Moayyedi, Robert Ridell, Philip Sherman, Sander van Zanten. The following people were participants of the consensus conference and are co-authors: Ivan Beck, Linda Best, Margaret Boland, Ford Bursey, Hugh Chaun, Geraldine Cooper, Brian Craig, Carole Creuzenet, Jeffrey Critch, Krishnasamy Govender, Eric Hassall, Alan Kaplan, Monica Keelan, Garth Noad, Marli Robertson, Lesley Smith, Markus Stein, Diane Taylor, Thomas Walters, Robin Persaud, Scott Whitaker, Robert Woodland.



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