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Update on Clinical Practice

Update on *Helicobacter pylori* Infection in Children

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Abstract *Helicobacter pylori* infection is a common worldwide infection. It is an important cause of gastric cancer, but an overwhelming majority of those get infected will not suffer any consequences during their lifetime. The indication of testing, diagnosis and management of this bacterial infection are also different in children and in adult. This article serves to highlight the important points included in the two guidelines, difference in management of adult and children patients, and discuss the applicability of the guidelines in the Hong Kong setting.

Key words Children; Diagnostic tests; Eradication; *Helicobacter pylori*; Triple therapy

Introduction

Helicobacter pylori (*H. pylori*) infection is a well-recognised aetiology for peptic ulcer disease and gastric cancer. The infection is often chronic and usually acquired in childhood, but it rarely causes complications in childhood and adolescence, in contrast to adults. Significant scientific advances have been made in this field throughout these years. The European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN)/ the North American Society of Paediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) and the American College of Gastroenterology (ACG) have issued new guidelines in management of this disease in 2016 and 2017.[1,2] This article serves to highlight the important points included in the two guidelines, difference in management of adult and children patients, and discuss the applicability of the guidelines in the Hong Kong setting.

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Who Should Be Tested and Treated?

All adult patients with an evidence of active *H. pylori* infection should be treated.[2] However, this statement may not be true in children.[1] In children with peptic ulcer disease, eradication of the infection may lower the risk of ulcer recurrence. For other situations, treatment is controversial. This is because there are no data showing that *H. pylori* cause symptoms or complications in children in the absence of peptic ulcer disease. *H. pylori* associated gastritis can be an incidental finding which is picked up during upper gastrointestinal endoscopy for work up of other conditions such as inflammatory bowel disease or coeliac disease, but this condition rarely gives rise to complications such as peptic ulcer disease and gastric cancer in childhood. Moreover, some young children can be re-infected with *H. pylori* after its successful eradication. A study in Bolivia has shown that the re-infection rate in 1 year can be up to 20% in young children.[1] Furthermore, there is epidemiological evidence for an inverse association between *H. pylori* infection and allergic diseases in young children.[1] Indeed, eradication of *H. pylori* in these children may not

relieve the symptoms, but may also expose the child to potential risk of treatment such as treatment failure, cramps, diarrhoea and undesirable alteration of the gut microbiome. Of course, in discussion with parents and older patient, these problems should be addressed as well as the risk of complications related to infection, such as peptic ulcer disease and gastric cancer, later in life.

For iron deficiency anaemia, testing and treatment of *H. pylori* remains controversial. A recently published systematic review and meta-analysis showed that there was a significantly increased likelihood of iron deficiency anaemia in *H. pylori* infected individuals compared with un-infected ones.[3] A study in Texas also found out that children with *H. pylori* infection eradicated had a significant 3-fold increase in ferritin over baseline level. However, such changes were not noted in a study conducted in Bangladesh.[4] A review in Iran concluded that there was not enough evidence to conclude that there was association of *H. pylori* eradication therapy and refractory childhood iron deficiency anaemia.[5]

Table 1 listed the indications of *H. pylori* testing and its treatment in adults and children:[1,2]

Table 1 Indications of *H. Pylori* testing and its treatment

Adults	**Children**
Testing indicated:	Testing indicated:
• Active peptic ulcer disease	• Active peptic ulcer disease
• Past history of peptic ulcer disease without cure of H. *pylori* infection documented	• Past history of peptic ulcer disease without cure of *H. pylori* infection documented
• Low grade gastric mucosa associated lymphoid tissue (MALT) lymphoma	• Refractory iron deficiency anaemia in which other causes have been ruled out (weak evidence)
• History of endoscopic resection of early gastric cancer	• Chronic immune thrombocytopenic purpura in childhood (weak evidence)
• Uninvestigated dyspepsia below the age of 60 without alarming features (point 1)	
• Patients taking long term low dose aspirin	
• Patients initiating chronic treatment with a non-steroidal anti-inflammatory drug (NSAID) (point 2)	
• Unexplained iron deficiency anaemia despite appropriate evaluation	
• Adults with idiopathic thrombocytopenic purpura	
Testing NOT indicated:	Testing NOT indicated:
• Typical symptoms of gastro-oesophageal reflux disease without history of peptic ulcer disease (GERD) (point 3)	• Functional abdominal pain disorders (point 4)
• Asymptomatic individuals with family history of gastric cancer	• Initial investigation of children with iron deficiency anaemia
	• Short stature

Note points:

1. Number needed to treat to cure functional dyspepsia was 14.
2. Benefit of testing and treating *H. pylori* in NSAID-treated patients remains unclear.
3. In the author's opinion, treatment of GERD may involve prolonged use of proton pump inhibitors (PPI), and eradication of *H. pylori* infection before starting this treatment may prevent the progression to atrophic gastritis.
4. Beware of warning signs, which include persistent right upper or right lower quadrant pain, dysphagia, odynophagia, persistent vomiting, gastrointestinal blood loss, involuntary weight loss, deceleration of linear growth, delayed puberty, unexplained fever, and a family history of inflammatory bowel disease, coeliac disease or peptic ulcer disease.[1]

Test and Treat Strategy

The ACG Guideline endorsed this treatment strategy for *H. pylori* infection for patients under 60 years of age who have dyspeptic symptoms and without warning features.[1] In areas that *H. pylori* is prevalent, non-invasive tests for this bacterium may be performed in this group of patients, and eradication therapy should be offered if test positive. Otherwise, the patient can be given a trial of proton pump inhibitors (PPI) and see if his or her symptoms will improve. In case of treatment failure in both situations, upper gastrointestinal endoscopy may then be arranged. The test and treat strategy was found to be more cost effective than proceeding with endoscopy right away or empirical acid suppression with PPI.[1] In children, as there was no data showing that *H. pylori* causes symptoms in the absence of peptic ulcer disease, if organic cause of dyspepsia is suspected, upper gastrointestinal endoscopy should be arranged. The test and treat strategy is not recommended.[2]

Diagnosis

In adults, diagnosis of *H. pylori* can be made easily by non-invasive tests such as urea breath tests and stool antigen test. The sensitivity and specificity of both tests are above 90%.[6] However, because of low prevalence of *H. pylori* infection in children, especially in Europe and North America, the positive predictive values of these tests are low. The ESPGHAN/NASPGHAN Guideline recommended that *H. pylori* infection in children should be diagnosed either by positive culture or by finding *H. pylori* gastritis on histopathology plus one more positive test such as rapid urease test (RUT). To achieve this diagnosis, the current standard is to obtain at least six gastric biopsies, including two from antrum and two from corpus for histopathological evaluation as well as one from antrum and one from corpus for *H. pylori* culture. One more gastric biopsy should be obtained for additional diagnostic test such as RUT. Urea breath test or stool antigen test may help to support the diagnosis of *H. pylori* infection.[1]

Note: The ACG Guideline recommends to collect biopsies of normal-appearing gastric mucosa for *H. pylori* detection during endoscopy in patients with dyspeptic symptoms; while the ESPGHAN/ NASPGHAN Guideline recommends that during endoscopy if antral nodularity without mucosal lesions (gastric/duodenal erosions or ulcers) is visualised, biopsies for RUT and culture to diagnose *H. pylori* infection and guide treatment should only be taken if treatment is likely to be offered upon confirmation of infection.

Treatment

Tables 2 and 3 summarised first line treatment options recommended by ESPGHAN/ NASPGHAN Guideline.[1]

For rescue therapy if first line treatment option fails,

Table 2 Treatment options recommended by ESPGHAN/ NASPGHAN

***H. pylori* antimicrobial susceptibility**	**Suggested treatment**
Known susceptibility to clarithromycin and to metronidazole	PPI + amoxicillin + clarithromycin for 14 days
Known resistance to clarithromycin but susceptibility to metronidazole	PPI + amoxicillin + metronidazole for 14 days or bismuth based
Known resistance to metronidazole but susceptibility to clarithromycin	PPI + amoxicillin + clarithromycin for 14 days or bismuth based
Resistance to both clarithromycin and metronidazole	PPI + amoxicillin + metronidazole for 14 days with high dose amoxicillin or bismuth based
Unknown	PPI + amoxicillin + metronidazole for 14 days with high dose amoxicillin or bismuth based, or concomitant therapy (PPI + amoxicillin + clarithromycin + metronidazole) for 14 days

* PPI dose 1.5-2.5 mg/kg/day refer to esomeprazole and omeprazole and should be adapted if other PPIs are used

Table 3 Standard dosing regimen as recommended by ESPGHAN/NASPGHAN Guideline[1]

Drug	Body weight range	Morning dose, mg	Evening dose, mg
PPI	15-24 kg	20	20
	25-34 kg	30	30
	35 kg or more	40	40
Amoxycillin	15-24 kg	500	500
	25-34 kg	750	750
	35 kg or more	1000	1000
Clarithromycin/metronidazole	15-24 kg	250	250
	25-34 kg	500	250
	35 kg or more	500	500

Table 4 First line treatment options recommended by ACG Guideline[2]

Name of regimen	Drug
Clarithromycin triple	PPI + clarithromycin + amoxicillin or metronidazole for 14 days (The only regimen approved by US Food and Drug Administration)
Bismuth quadruple	PPI + bismuth + tetracycline + metronidazole for 10-14 days
Concomitant	PPI + clarithromycin + amoxicillin + nitroimidazole for 10-14 days
Sequential	PPI + amoxicillin for 5-7 days then PPI + clarithromycin + nitroimidazole for 5-7 days
Hybrid	PPI + amoxicillin for 7 days then PPI + amoxycillin + clarithromycin + nitroimidazole for 7 days
Levofloxacin triple	PPI + levofloxacin + amoxicillin for 10-14 days
Levofloxacin sequential	PPI + amoxicillin for 5-7 days then PPI + levofloxacin + nitroimidazole for 5-7 days
LOAD	Levofloxacin + PPI double dose + nitazoxanide + doxycycline for 7-10 days

please refer to the original guidelines for details.

The ACG Guideline recommends enquiry of patients' previous antibiotic exposure, particularly macrolides and fluoroquinolones, when choosing a treatment regimen (Table 4). Previous macrolide therapy for longer than 2 weeks in 20 years is associated with higher risk of treatment failure with clarithromycin triple therapy.[7,8] For those with reported penicillin allergy and failed first line *H. pylori* eradication therapy, the ACG Guideline recommends that these patients should be referred for allergy testing since the vast majority, who do not have true penicillin hypersensitivity, can ultimately be safely given amoxicillin-containing salvage regimens.[2] Enquiry about previous antibiotic exposure and penicillin allergy testing are not mentioned in the paediatric guidelines but the author believes that these are good practice (and paediatricians should consider to follow).

The ESPGHAN/NASPGHAN Guideline mentioned that levofloxacin or tetracycline may be considered in the rescue regimen if an adolescent patient failed treatment with first line therapy options. Paediatricians may worry about the safety profile of these two groups of drugs. A study published in 2014 has shown that levofloxacin may be safe for use in children.[9] Doxycycline has been used for treatment of macrolide resistant *Mycoplasma pneumoniae* in children and so-far no significant adverse events have been reported.[10]

Outcome Assessment

The ACG and the ESPGHAN/ NASPGHAN Guidelines recommend testing to prove eradication of *H. pylori* at least 4 weeks after completion of antibiotic therapy, and after

PPI therapy have been withheld for two weeks. This may be carried out by the urea breath test or stool antigen test.[1,2]

Probiotic

The ESPGHAN/NASPGHAN Guideline does not support the routine addition of probiotic to *H. pylori* eradication therapies due to the lack of evidence that this treatment can reduce the side effects.

Further Research Questions

A study published in 2008 involving 2480 Hong Kong children aged 6-19 years has shown that 13.1% of the population had positive urea breath test that suggested *H. pylori* infection.[11] A continuous surveillance of the situation is needed as disease prevalence will affect the positive predictive value and cost effectiveness of different diagnostic tests, as well as our recommendation in diagnosing *H. pylori* infection among local children.

Research should also be conducted on whether the test and treat strategy is suitable for management of Hong Kong adolescents with apparent dyspepsia. Dyspeptic symptoms are not uncommon in adolescents in Hong Kong, and *H. pylori* infection is much more prevalent in Hong Kong than in countries in Europe and North America.[12,13] This may be a cost-effective strategy in the management of this group of patients.

Applicability

Although the prevalence of *H. pylori* infection in children is different, there are similarities between the situation in Hong Kong and that in Europe and North America (Table 5). There are no data showing that *H. pylori* cause symptoms or complications in children in the absence of peptic ulcer disease in Hong Kong, Europe and North America. Due to the even higher prevalence of *H. pylori* infection in Hong Kong, the risk of re-infection after eradication may even be higher. There is so far no evidence that eradication of *H. pylori* infection in childhood can lower the risk of stomach cancer in adulthood in Hong Kong. Therefore the author believed that the Joint ESPGHAN/NASPGHAN Guideline can be applied in Hong Kong.

Table 5 Prevalence of *Helicobacter pylori* infection in children

Area	Prevalence estimates
Hong Kong	13.1%[11]
Iran	64.2%[14]
United Kingdom	Less than 5%[15]
Turkey	23.6%[16]
United States	Less than 5%[16]

Summary

1. Management of *H. pylori* infection is different between adults and children because of different treatment aims, different risk of disease complications such as peptic ulcer disease and gastric cancer, and different re-infection rate.
2. *H. pylori* associated gastritis without peptic ulcer disease does not cause symptoms in most children. Therefore, treatment of such condition may not relieve the gastrointestinal symptoms of children. Children with functional abdominal pain should not undergo testing for *H. pylori* infection.
3. The traditional 7-day triple therapy regimen should not be used to eradicate *H. pylori* in view of its low efficacy. The ACG Guideline recommends that triple therapy should be given for 14 days in the North America.[2]

Competing Interest

None declared.

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