Nuove linee guida sull’infezione da Helicobacter Pylori

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What’s the story *H pylori*?

“SPIROCHETES" INHABITING THE GASTRIC GLANDS OF DOGS


Letters to the Editor UNIDENTIFIED CURVED BACILLI ON GASTRIC EPITHELIUM IN ACTIVE CHRONIC GASTRITIS

Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration

• Biopsy specimens were taken from intact areas of antral mucosa in 100 consecutive consenting patients presenting for gastroscopy.

• Spiral or curved bacilli were demonstrated in specimens from 58 patients.

• Bacilli cultured from 11 of these biopsies were gram-negative, flagellate, and microaerophilic and appeared to be a new species related to the genus Campylobacter.

• The bacteria were present in almost all patients with active chronic gastritis, duodenal ulcer, or gastric ulcer and thus may be an important factor in the aetiology of these diseases.

The Nobel Prize in Physiology or Medicine 2005

"for their discovery of the bacterium *Helicobacter pylori* and its role in gastritis and peptic ulcer disease"

Barry J. Marshall
Australia
b. 1951

J. Robin Warren
Australia
b. 1937
The prevalence of *H pylori* infection in children in southern Italy has been reported to be 23%.

Incidence rates of *H pylori infection* in children varies from 1.7% to 15%.

Young children with *H pylori* are infected before the age of 3 years and that the risk of infection is very low after 5 years of age.

Risk factors

- Childhood socioeconomic status of the mothers
- Infected mother
- Infected older sibling
- Delayed weaning from a feeding bottle (ie, after 24 months of age)
Pathogenesis of *H. pylori* Infection
Pathogen-Host Interactions in the Pathogenesis of *H. pylori* Infection
Diseases associated with *H. pylori*
Clinical Complications of *H. pylori* Infection
Nodular gastritis and Helicobacter pylori infection in childhood

- Chronic type B gastritis
- Antral Nodular Gastritis
  - Children: 30-100%
  - Adults: less frequent

ANNALS OF GASTROENTEROLOGY 2000, 13(2):138-141
Clinical Complications of *H. pylori* Infection

**H. pylori** Infection Prevalence

<table>
<thead>
<tr>
<th>Condition</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duodenal Ulcers</td>
<td>92%</td>
<td>33%-100%</td>
</tr>
<tr>
<td>Gastric Ulcers</td>
<td>25%</td>
<td>11%-75%</td>
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</table>

Low rate (<5% to 10%) of disease recurrence in children treated and cured of the bacterial infection

*Jama* 1995; 273: 729-734  
*Arch Dis Child* 1998; 79: 502-505
The role of *H. pylori* in the cause of recurrent abdominal pain (RAP) and other gastrointestinal symptoms (GI) remains controversial.

- No association between RAP and *H pylori* infection in children.

- Conflicting evidence for an association between epigastric pain and *H pylori* infection.

- Evidence for an association between unspecified abdominal pain but this finding in children seen in primary care could not be confirmed.

- Periumbilical pain, flatus, constipation, nausea, loose stools, postprandial fullness, halitosis, dyspepsia, and regurgitation, were not associated with *H pylori* infection.

*Pediatrics* 2010;125;e651;
Extraintestinal Manifestations

• Increasing body of literature supports an association between *Helicobacter pylori* infection and iron-deficiency anemia in children and adults.

• The definitive mechanism(s) of iron deficiency anemia in those infected with *H pylori* is unclear:
  - Gastrointestinal blood loss?
  - Poor iron intake?
  - Iron malabsorption?
  - Diversion of iron in the reticuloendothelial system?
  - Bacteria-specific mechanism(s)?

*Pediatrics* 2010;125;e651;
Who Should Be Tested?
Who Should Be Tested?

- The primary goal of clinical investigation of gastrointestinal symptoms is to determine the underlying cause of the symptoms and not solely the presence of *H pylori* infection.

- Diagnostic testing for *H pylori* infection is not recommended in children with functional abdominal pain.

- There is insufficient evidence that *H pylori* infection is causally related to otitis media, upper respiratory tract infections, periodontal disease, food allergy, SIDS, idiopathic thrombocytopenic purpura, and short stature.
Who Should Be Tested?

• In children with first-degree relatives with gastric cancer, testing for *H pylori* may be considered.

• In children with refractory iron-deficiency anemia in which other causes have been ruled out, testing for *H pylori* infection may be considered.
Which Diagnostic Test Should Be Applied in Which Situation?
### Helicobacter Pylori Infection: Diagnostic Tests

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Costs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Noninvasive Tests</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Antibodies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whole Blood</td>
<td>70-85</td>
<td>75-90</td>
<td>$</td>
</tr>
<tr>
<td>Serum</td>
<td>86-94</td>
<td>75-90</td>
<td>$</td>
</tr>
<tr>
<td>ELISA</td>
<td>86-94</td>
<td>80-95</td>
<td>$$</td>
</tr>
<tr>
<td>Fecal Antigens</td>
<td>88-98</td>
<td>89-98</td>
<td>$$</td>
</tr>
<tr>
<td>¹³C-Urea Breath test</td>
<td>90-96</td>
<td>88-98</td>
<td>$$$</td>
</tr>
<tr>
<td><strong>Invasive tests</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biopsy with CLOTest</td>
<td>90-95</td>
<td>95-100</td>
<td>$$$$</td>
</tr>
<tr>
<td>Histology</td>
<td>90-95</td>
<td>95-100</td>
<td>$$$$$</td>
</tr>
<tr>
<td>Culture</td>
<td>60-95</td>
<td>100</td>
<td>$$$$$</td>
</tr>
</tbody>
</table>
Which Diagnostic Test Should Be Applied in Which Situation?

- For the diagnosis of H pylori infection during EGD, it is recommended that gastric biopsies (antrum and corpus) for histopathology are obtained.

- It is recommended that the initial diagnosis of H pylori infection be based on either positive histopathology + positive rapid urease test or a positive culture.

- It is recommended that clinicians wait at least 2 weeks after stopping PPI therapy and 4 weeks after stopping antibiotics to perform biopsy-based and noninvasive tests (UBT, stool test) for H pylori.

*JPGN* 2011;53: 230–243
Which Diagnostic Test Should Be Applied in Which Situation?

- The 13C-UBT is a reliable noninvasive test to determine whether \textit{H. pylori} has been eradicated.

- A validated ELISA for detection of \textit{H. pylori} antigen in stool is a reliable noninvasive test to determine whether \textit{H. pylori} has been eradicated.

- Tests based on the detection of antibodies (IgG, IgA) against \textit{H. pylori} in serum, whole blood, urine, and saliva are not reliable for use in the clinical setting.
Who Should Be Treated?
THE TEST-AND-TREAT STRATEGY

*Statement 1:* A test-and-treat strategy is appropriate for uninvestigated dyspepsia in populations where the *H pylori* prevalence is high (>20%). This approach is subject to local cost-benefit considerations and is not applicable to patients with alarm symptoms, or older patients (age to be determined locally according to cancer risk)

**Evidence level: 1a**  
**Grade of recommendation: A**

*Statement 2:* The main non-invasive tests that can be used for the test-and-treat strategy are the UBT and monoclonal stool antigen tests. Certain validated serological tests can also be used.

**Evidence level: 2a**  
**Grade of recommendation: B**

*Gut* 2012;61:646e664.
Who Should Be Treated?

• In the presence of *H pylori*–positive PUD, eradication of the organism is recommended.

• When *H pylori* infection is detected by biopsy-based methods in the absence of PUD, *H pylori* treatment may be considered.

• In children who are infected with *H pylori* and whose first-degree relative has gastric cancer, treatment can be offered.

• A “test and treat” strategy is not recommended in children.
Helicobacter pylori Chronic Gastritis in Children: To Eradicate or Not to Eradicate?

Roberta Buonavolontà, MD, Erasmo Miele, MD, PhD, Daniela Russo, MD, Raffaella Vecchione, MD, and Annamaria Staiano, MD

![Graph showing comparison between eradication therapy and symptomatic therapy for Chronic Inflammation, Activity, and HP density at T0 and T2, with statistical significance values for each category.](image-url)
Which Treatment Should Be Applied in Which Situation?
Meta-analysis: *Helicobacter pylori* eradication treatment efficacy in children

- Most evidence and recommendations for the treatment of *H. pylori* infection have been derived from adult data.

- Majority of paediatric studies have come from single centre case series and reports that include relatively small numbers of patients.

- However, as many treatment options have not yet been formally tested in children, especially in developing countries, further studies are needed.

*Aliment Pharmacol Ther 2007; 25, 523–536*
First-line treatment recommendations for *H pylori* eradication in children

- **PPI (1–2 mg·kg\(^{-1}\)·day\(^{-1}\)) + amoxicillin (50 mg·kg\(^{-1}\)·day\(^{-1}\)) + metronidazole (20 mg·kg·day)\(^{*}\)**
- **PPI (1–2 mg·kg\(^{-1}\)·day\(^{-1}\)) + amoxicillin (50 mg·kg\(^{-1}\)·day\(^{-1}\)) + clarithromycin (20 mg·kg\(^{-1}\)·day\(^{-1}\))\(^{*}\)**
- **Bismuth salts (bismuth subsalicylate or subcitrate 8 mg·kg\(^{-1}\)·day\(^{-1}\)) + amoxicillin (50 mg·kg\(^{-1}\)·day\(^{-1}\)) + metronidazole (20 mg·kg\(^{-1}\)·day\(^{-1}\))\(^{*}\)**
- **PPI (1–2 mg·kg\(^{-1}\)·day\(^{-1}\)) + amoxicillin (50 mg·kg\(^{-1}\)·day\(^{-1}\)) for 5 days then PPI (1–2 mg·kg\(^{-1}\)·day\(^{-1}\)) + clarithromycin (20 mg·kg\(^{-1}\)·day\(^{-1}\)) + metronidazole (20 mg·kg\(^{-1}\)·day\(^{-1}\)) for 5 days**

Maximum daily dose for amoxicillin 2000 mg, for metronidazole 1000 mg/day. PPI = proton pump inhibitor.

*Administered twice daily for 10 to 14 days.*

*JPGN 2011;53: 230–243*
Recommendations for \textit{H pylori} eradication

- A reliable noninvasive test for eradication is recommended at least 4 to 8 weeks following completion of therapy.

- Antibiotic susceptibility testing for clarithromycin is recommended before initial clarithromycin based triple therapy in areas/populations with a known high resistance rate (>20%) of \textit{H pylori} to clarithromycin.

- It is recommended that the duration of triple therapy be 7 to 14 days. Costs, compliance, and adverse effects should be taken into account.

\textit{JPGN} 2011;53: 230–243
Worldwide *H. pylori* Antibiotic Resistance: a Systematic Review

Antibiotic resistance rates in different continental areas

<table>
<thead>
<tr>
<th>Area</th>
<th>Amoxycillin</th>
<th>Clarithromycin</th>
<th>Metronidazole</th>
<th>Tetracycline</th>
<th>Levofoxacin</th>
<th>Multidrugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>America</td>
<td>8/352</td>
<td>118/402</td>
<td>177/401</td>
<td>11/393</td>
<td>NA</td>
<td>53/352</td>
</tr>
<tr>
<td></td>
<td>(2.2%)</td>
<td>(29.3%)</td>
<td>(44.1%)</td>
<td>(2.7%)</td>
<td></td>
<td>(15.0%)</td>
</tr>
<tr>
<td>Africa</td>
<td>113/172</td>
<td>NA</td>
<td>159/172</td>
<td>58/132</td>
<td>0/40</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>(65.6%)</td>
<td></td>
<td>(92.4%)</td>
<td>(43.9%)</td>
<td>(0.0%)</td>
<td></td>
</tr>
<tr>
<td>Asia</td>
<td>60/517</td>
<td>1,544/8,139</td>
<td>192/517</td>
<td>11/456</td>
<td>106/908</td>
<td>21/252</td>
</tr>
<tr>
<td></td>
<td>(11.6%)</td>
<td>(18.9%)</td>
<td>(37.1%)</td>
<td>(2.4%)</td>
<td>(11.6%)</td>
<td>(8.3%)</td>
</tr>
<tr>
<td>Europe</td>
<td>3/599</td>
<td>352/3156</td>
<td>420/2,459</td>
<td>14/599</td>
<td>148/614</td>
<td>204/2,272</td>
</tr>
<tr>
<td></td>
<td>(0.5%)</td>
<td>(11.1%)</td>
<td>(17.0%)</td>
<td>(2.1%)</td>
<td>(24.1%)</td>
<td>(8.9%)</td>
</tr>
<tr>
<td>Overall</td>
<td>184/1,640</td>
<td>2,014/11,697</td>
<td>948/3,549</td>
<td>94/1,580</td>
<td>254/1,562</td>
<td>278/2,876</td>
</tr>
<tr>
<td></td>
<td>(11.2%)</td>
<td>(17.2%)</td>
<td>(26.7%)</td>
<td>(5.9%)</td>
<td>(16.2%)</td>
<td>(9.6%)</td>
</tr>
</tbody>
</table>

*J Gastrointestin Liver Dis* 2010 ;19: 409-414
If treatment has failed?

1. EGD, with culture and susceptibility testing, including alternate antibiotics if not performed before guide therapy.

2. FISH on previous paraffin-embedded biopsies if clarithromycin susceptibility testing has not been performed before guide therapy.

3. Modify therapy by adding an antibiotic, using different antibiotics, adding bismuth, and/or increasing dose and/or duration of therapy.
Second Line Treatment

- Quadruple therapy: PPI + metronidazole + amoxicillin + bismuth.

- Triple therapy: PPI + levofloxacin (moxifloxacin) + amoxicillin.
What I Learned From...
Helicobacter pylori Infection in Children

Take Home Messages

• *H pylori* is an important human pathogen that is a significant source of gastroduodenal disease in adults as well as children.

• Specific symptoms suggestive of *H pylori* infection are vague, inconsistent, and similar to several other more common childhood disorders, manifesting as recurrent abdominal pain, dyspepsia, or epigastric pain.

• Generally, one does not investigate for *H pylori* unless the child has symptoms suggestive of an ulcer.
Although several noninvasive tests have been evaluated, endoscopy with gastric biopsy is, at present, considered the gold standard to confirming the diagnosis of *H pylori*.

H pylori infection can be eradicated by antimicrobial therapy, but no treatment regimen is 100% effective.

Multiple drugs, frequent dosing, and length of treatment often contribute to poor patient compliance, and antibiotic eradication therapy is associated with increasing drug resistance.
APPLAUSI!