

XXIV Congresso Nazionale  
Società Italiana di Pediatria  
Preventiva e Sociale

# BAMBINI DI VETRO

12 - 15  
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Caserta



## Nuove linee guida sull'infezione da *Helicobacter Pylori*

*Erasmus Miele*

Dipartimento di Pediatria  
Università di Napoli "Federico II"

[erasmo.miele@unina.it](mailto:erasmo.miele@unina.it)



# What's the story *H pylori* ?

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"SPIROCHETES" INHABITING  
THE GASTRIC GLANDS OF DOGS



Giulio Bizzozero, *Arch. Mikr. Anat.* **1893**; **42**: 82-152

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



J Robin Warren, Barry Marshall. *Lancet.* **1983**; **1**:1273-5

## THE LANCET

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

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- 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

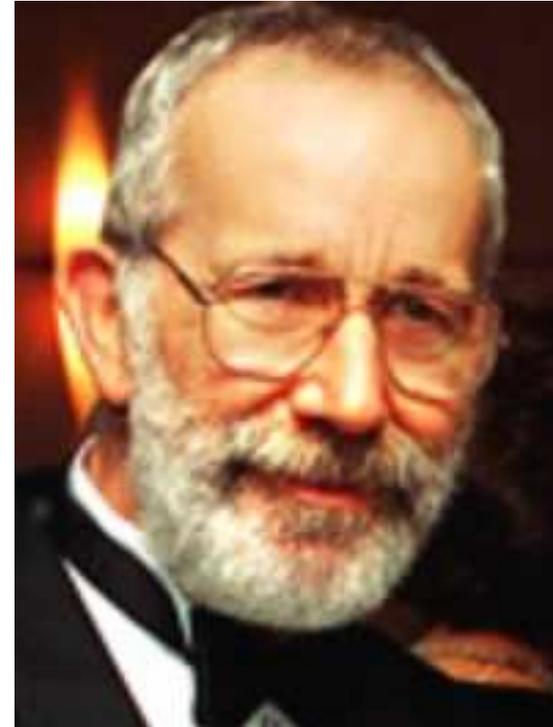
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"for their discovery of the bacterium *Helicobacter pylori* and its role in gastritis and peptic ulcer disease"



**Barry J. Marshall**  
**Australia**

b. 1951

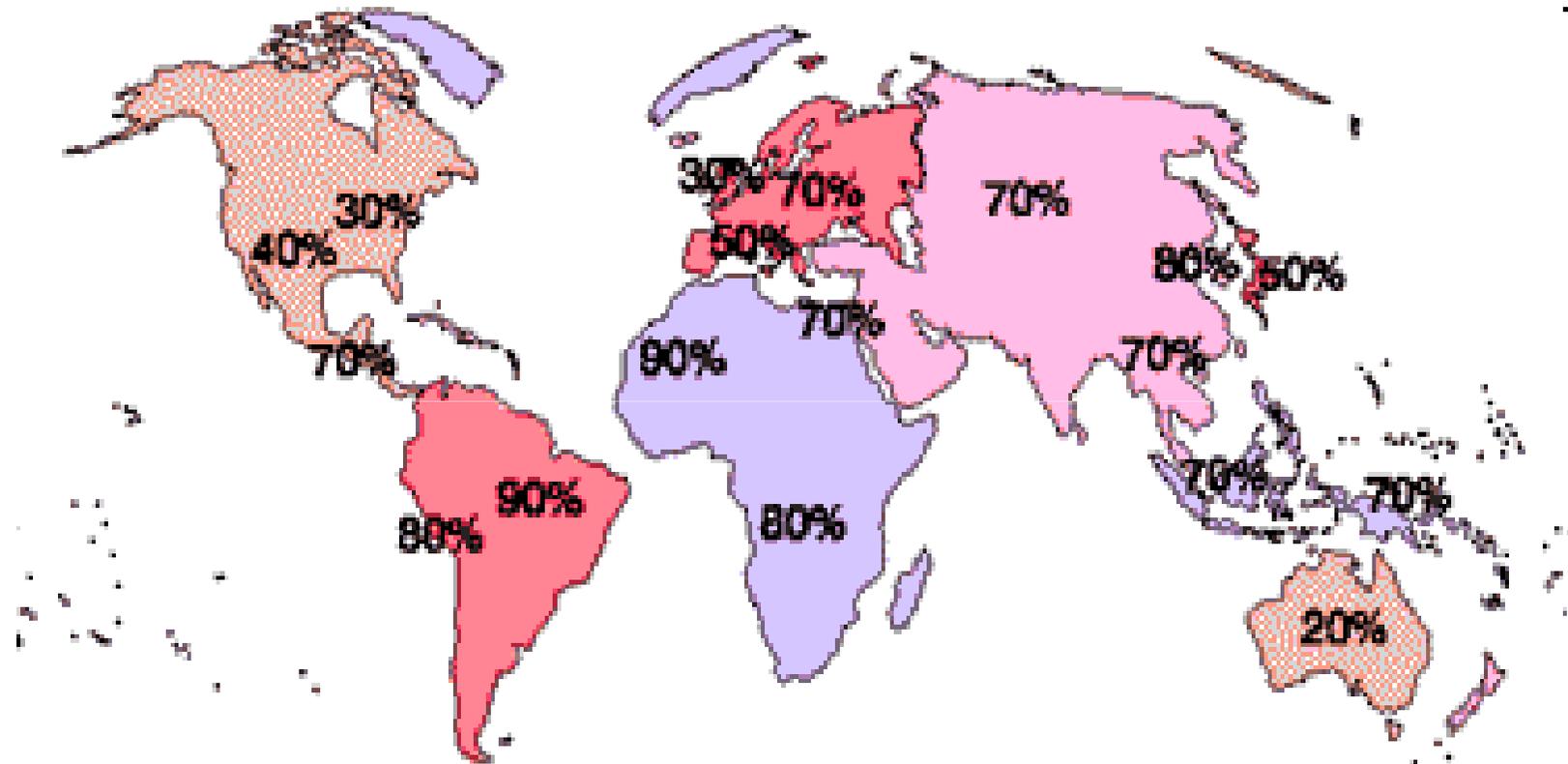


**J. Robin Warren**  
**Australia**

b. 1937

# Areas with *H. Pylori*

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The prevalence of *H pylori* infection in children in southern Italy has been reported to be 23%

Perri F, et al *Arch Dis Child*. 1997;77:46–49

# Age-Specific Incidence of *Helicobacter pylori*



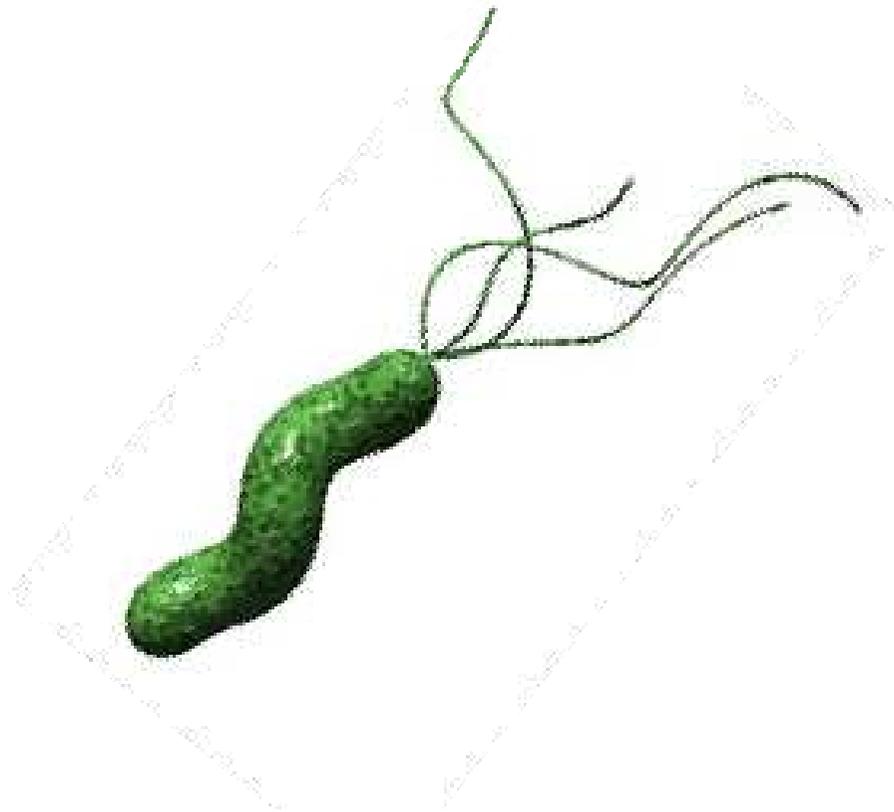
MARION ROWLAND,\* LESLIE DALY,<sup>†</sup> MARIAN VAUGHAN,\* ANNA HIGGINS,\* BILLY BOURKE,\*<sup>§,||</sup>  
and BRENDAN DRUMM\*<sup>§,||</sup>

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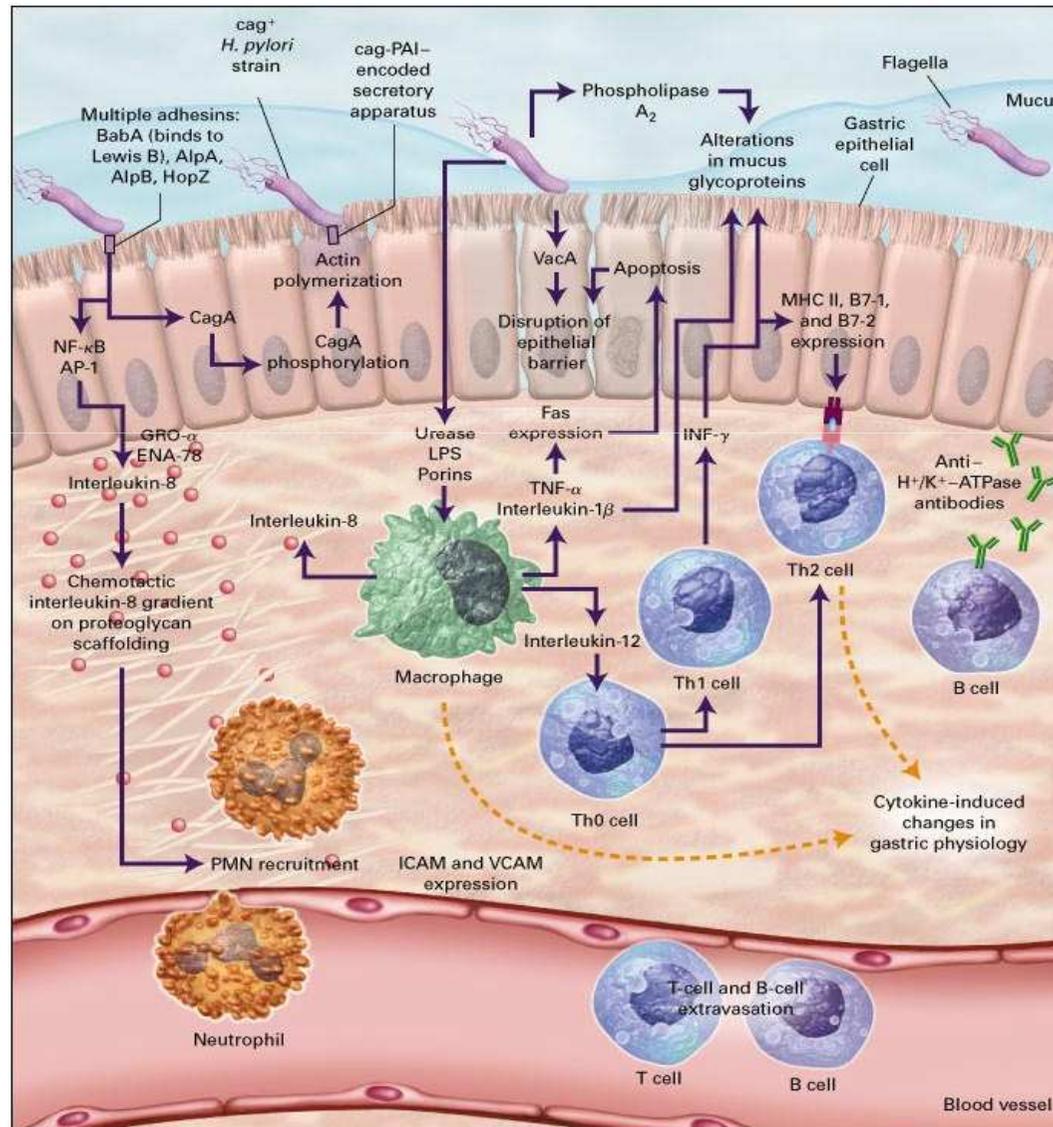
- Incidence rates of *H pylori infection* in children varies from 1.7% to 15%.
- Young children with *H pylori* are infected before the age of 3 years and that the risk of infection is very low after 5 years of age.
- Risk factors
  - Childhood socioeconomic status of the mothers
  - Infected mother
  - Infected older sibling
  - Delayed weaning from a feeding bottle (ie, after 24 months of age)

# Pathogenesis of *H. pylori* Infection

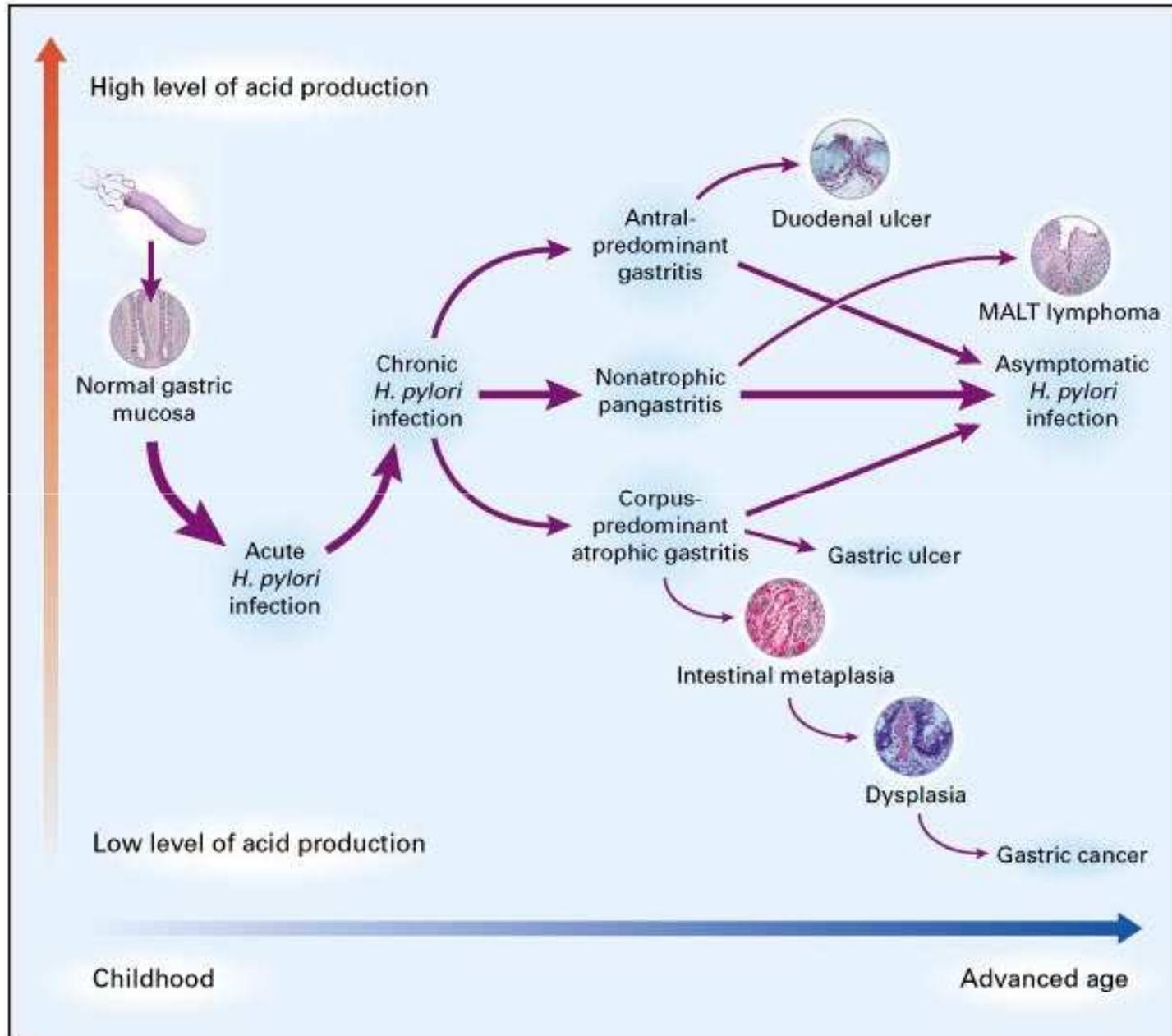
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# Pathogen-Host Interactions in the Pathogenesis of *H. pylori* Infection

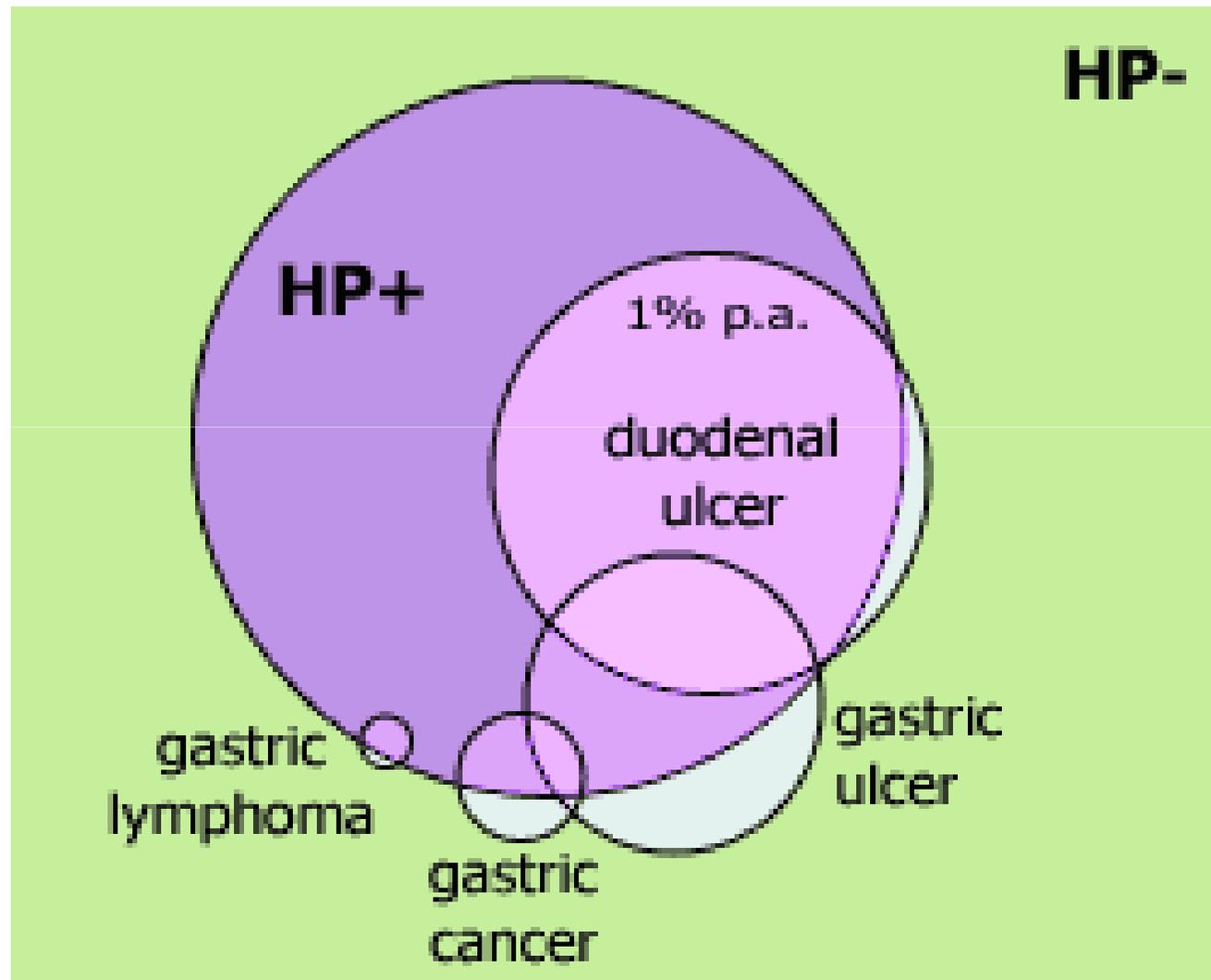


# Natural History of *H. pylori* Infection



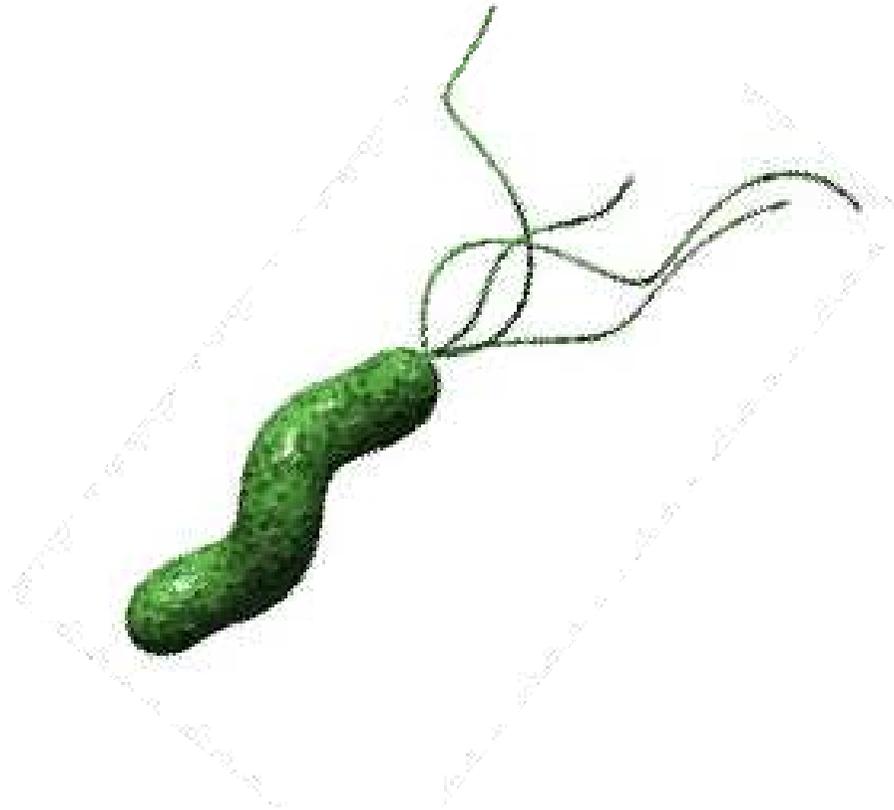
# Diseases associated with *H. pylori*

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# Clinical Complications of *H. pylori* Infection

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# Nodular gastritis and *Helicobacter pylori* infection in childhood

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- Chronic type B gastritis
- Antral Nodular Gastritis

Children: 30-100%

Adults: less frequent



# Clinical Complications of *H. pylori* Infection

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## *H. pylori* Infection Prevalence

	Median	Range
• Duodenal Ulcers	92%	33%-100%
• Gastric Ulcers	25%	11%-75%

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

# Association Between *Helicobacter pylori* and Gastrointestinal Symptoms in Children

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- 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.

# Association Between *Helicobacter pylori* and Gastrointestinal Symptoms in Children

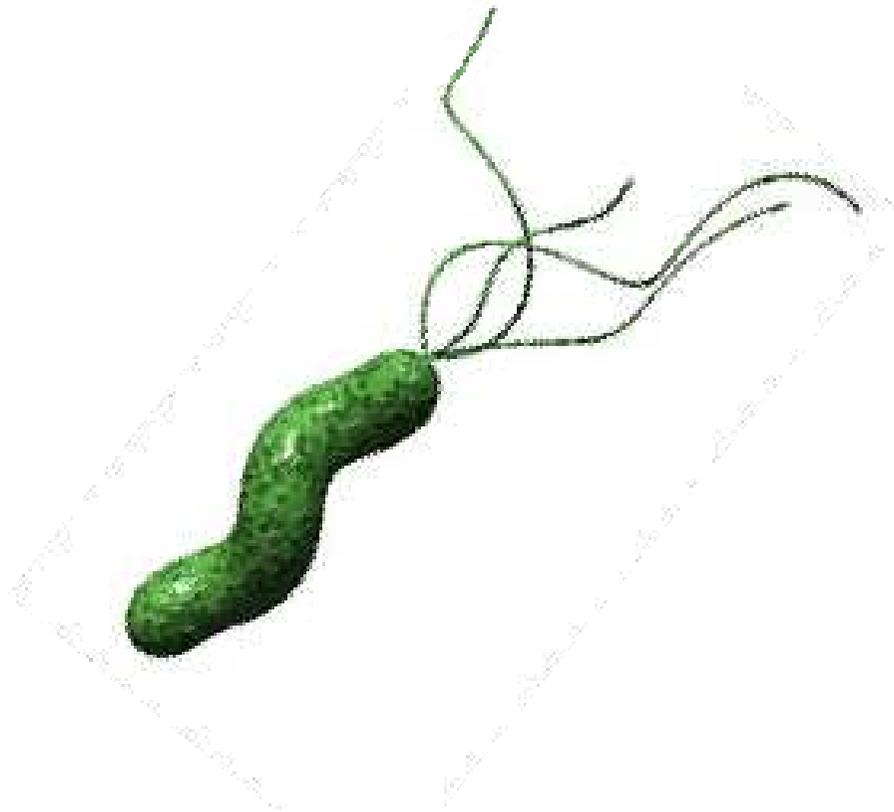
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## Extraintestinal Manifestations

- Increasing body of literature supports an association between *H 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)?

# Who Should Be Tested?

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## Evidence-based Guidelines From ESPGHAN and NASPGHAN for *Helicobacter pylori* Infection in Children



### 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.

## Evidence-based Guidelines From ESPGHAN and NASPGHAN for *Helicobacter pylori* Infection in Children

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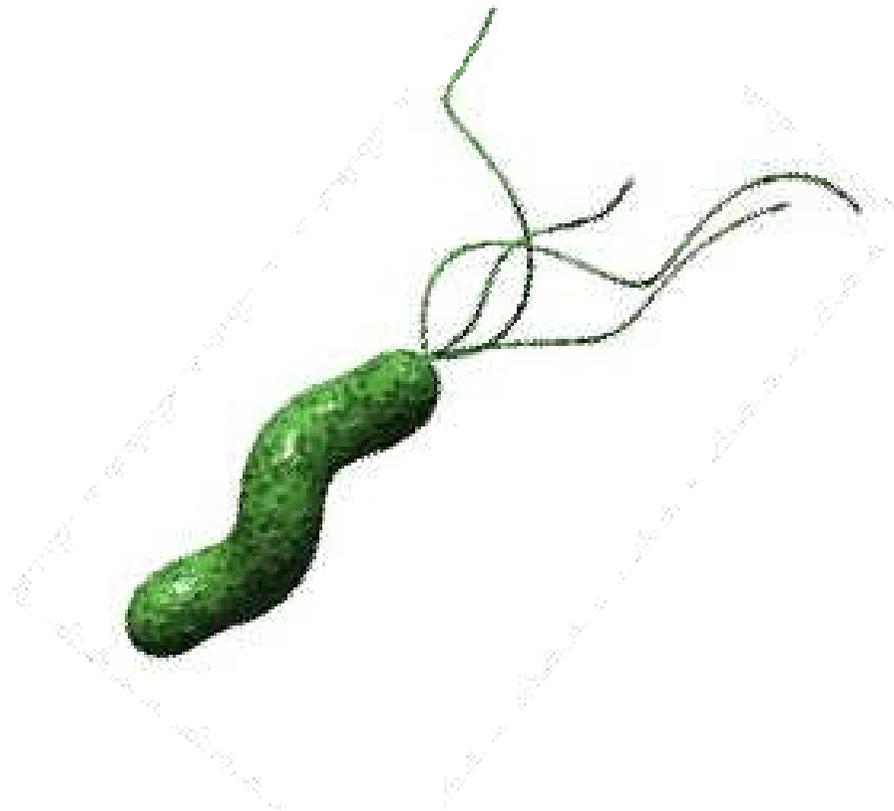
### Who Should Be Tested?



- 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?

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# Helicobacter Pylori Infection: Diagnostic Tests

<b>Test</b>	<b>Sensitivity</b>	<b>Specificity</b>	<b>Costs</b>
<b>Noninvasive Tests</b>			
Antibodies			
Whole Blood	70-85	75-90	\$
Serum	86-94	75-90	\$
ELISA	86-94	80-95	\$\$
Fecal Antigens	88-98	89-98	\$\$
<sup>13</sup> C-Urea Breath test	90-96	88-98	\$\$\$
<b>Invasive tests</b>			
Biopsy with CLOTest	90-95	95-100	\$\$\$\$
Histology	90-95	95-100	\$\$\$\$\$
Culture	60-95	100	\$\$\$\$\$

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## Evidence-based Guidelines From ESPGHAN and NASPGHAN for *Helicobacter pylori* Infection in Children

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ESPGHAN

### 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.

## Evidence-based Guidelines From ESPGHAN and NASPGHAN for *Helicobacter pylori* Infection in Children



ESPGHAN

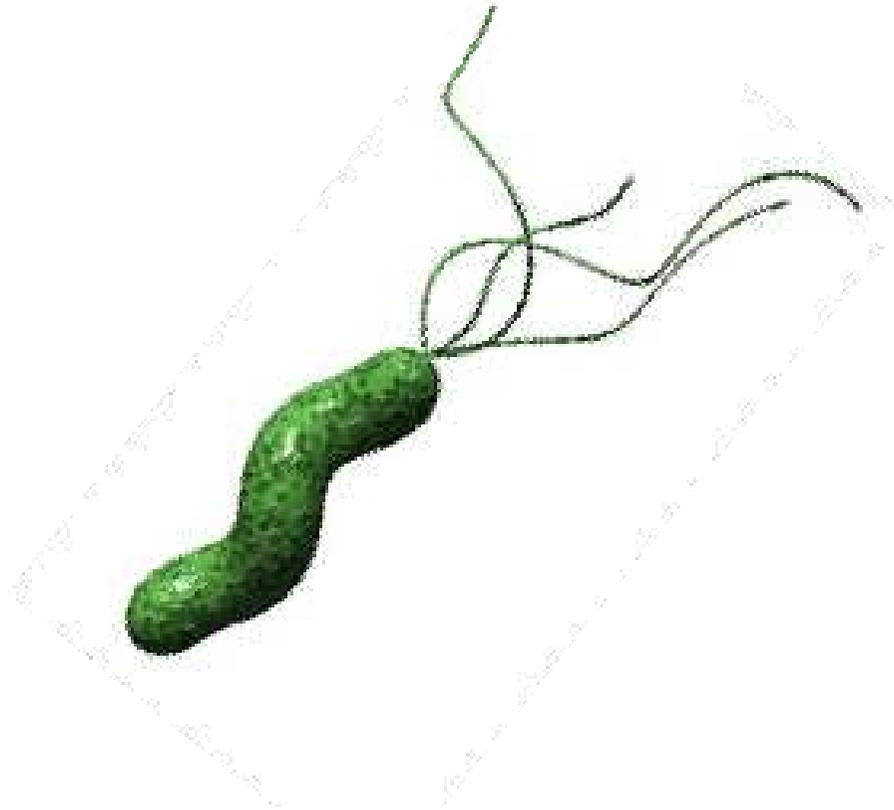
### Which Diagnostic Test Should Be Applied in Which Situation?



- The  $^{13}\text{C}$ -UBT is a reliable noninvasive test to determine whether *H pylori* has been eradicated.
- A validated ELISA for detection of *H. pylori* antigen in stool is a reliable noninvasive test to determine whether *H pylori* has been eradicated
- Tests based on the detection of antibodies (IgG, IgA) against *H pylori* in serum, whole blood, urine, and saliva are not reliable for use in the clinical setting

# Who Should Be Treated?

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## Management of *Helicobacter pylori* infection—the Maastricht IV/ Florence Consensus Report

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### 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**

# Evidence-based Guidelines From ESPGHAN and NASPGHAN for *Helicobacter pylori* Infection in Children



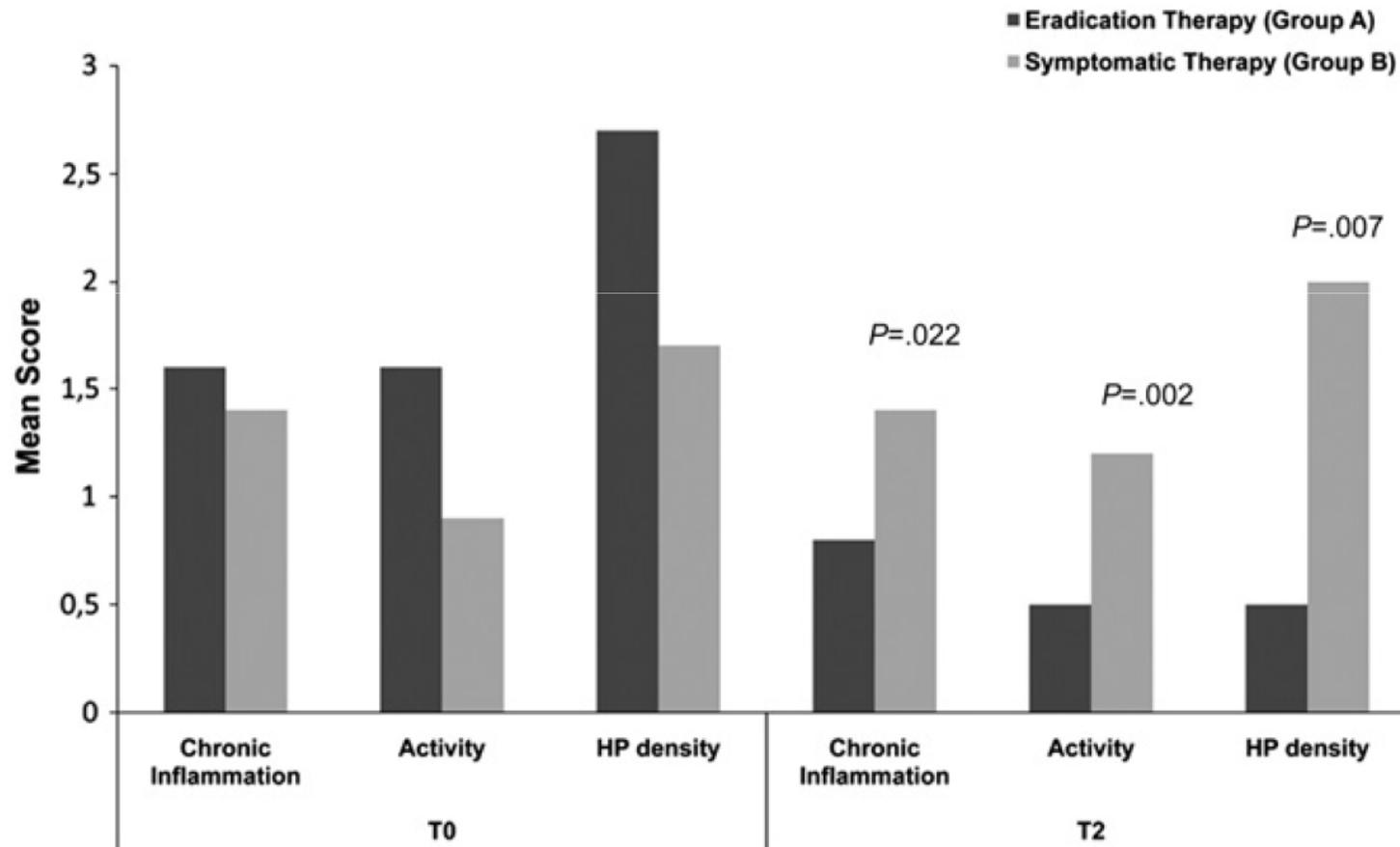
## Who Should Be Treated?



- 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.

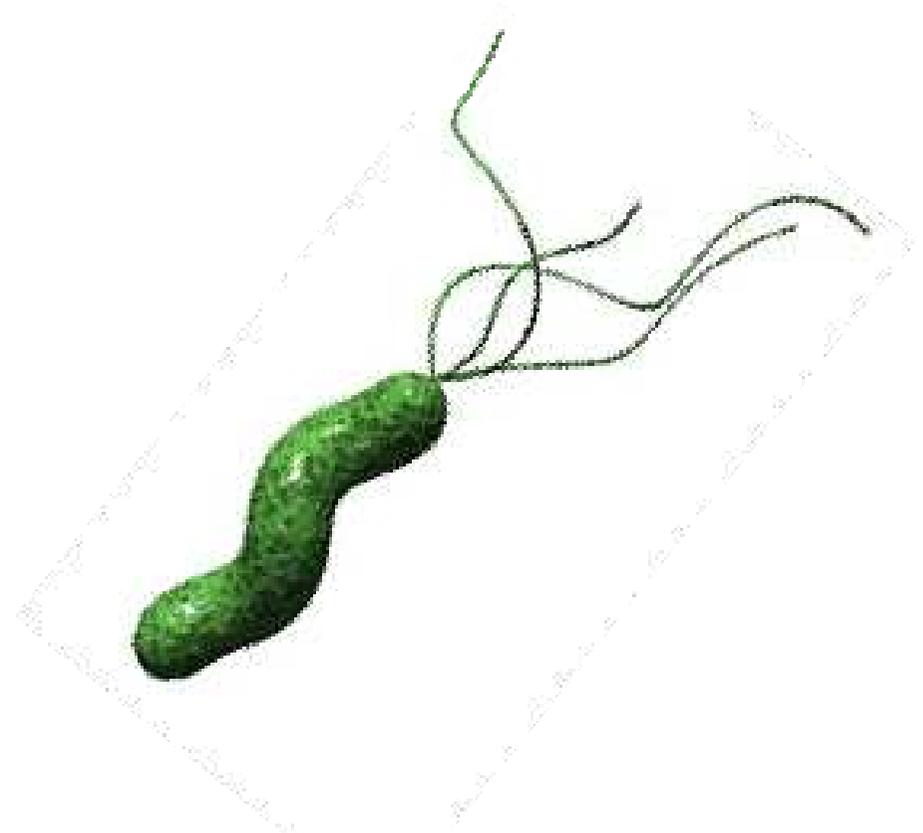
## *Helicobacter pylori* Chronic Gastritis in Children: To Eradicate or Not to Eradicate?

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



# Which Treatment Should Be Applied in Which Situation?

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## Meta-analysis: *Helicobacter pylori* eradication treatment efficacy in children

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- 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.

# Evidence-based Guidelines From ESPGHAN and NASPGHAN for *Helicobacter pylori* Infection in Children



## First-line treatment recommendations for *H pylori* eradication in children



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



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

\* Administered twice daily for 10 to 14 days.

## Evidence-based Guidelines From ESPGHAN and NASPGHAN for *Helicobacter pylori* Infection in Children



Recommendations for *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 *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.

## REVIEWS

# Worldwide *H. pylori* Antibiotic Resistance: a Systematic Review

## Antibiotic resistance rates in different continental areas

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

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## Evidence-based Guidelines From ESPGHAN and NASPGHAN for *Helicobacter pylori* Infection in Children

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### 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.

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# Evidence-based Guidelines From ESPGHAN and NASPGHAN for *Helicobacter pylori* Infection in Children

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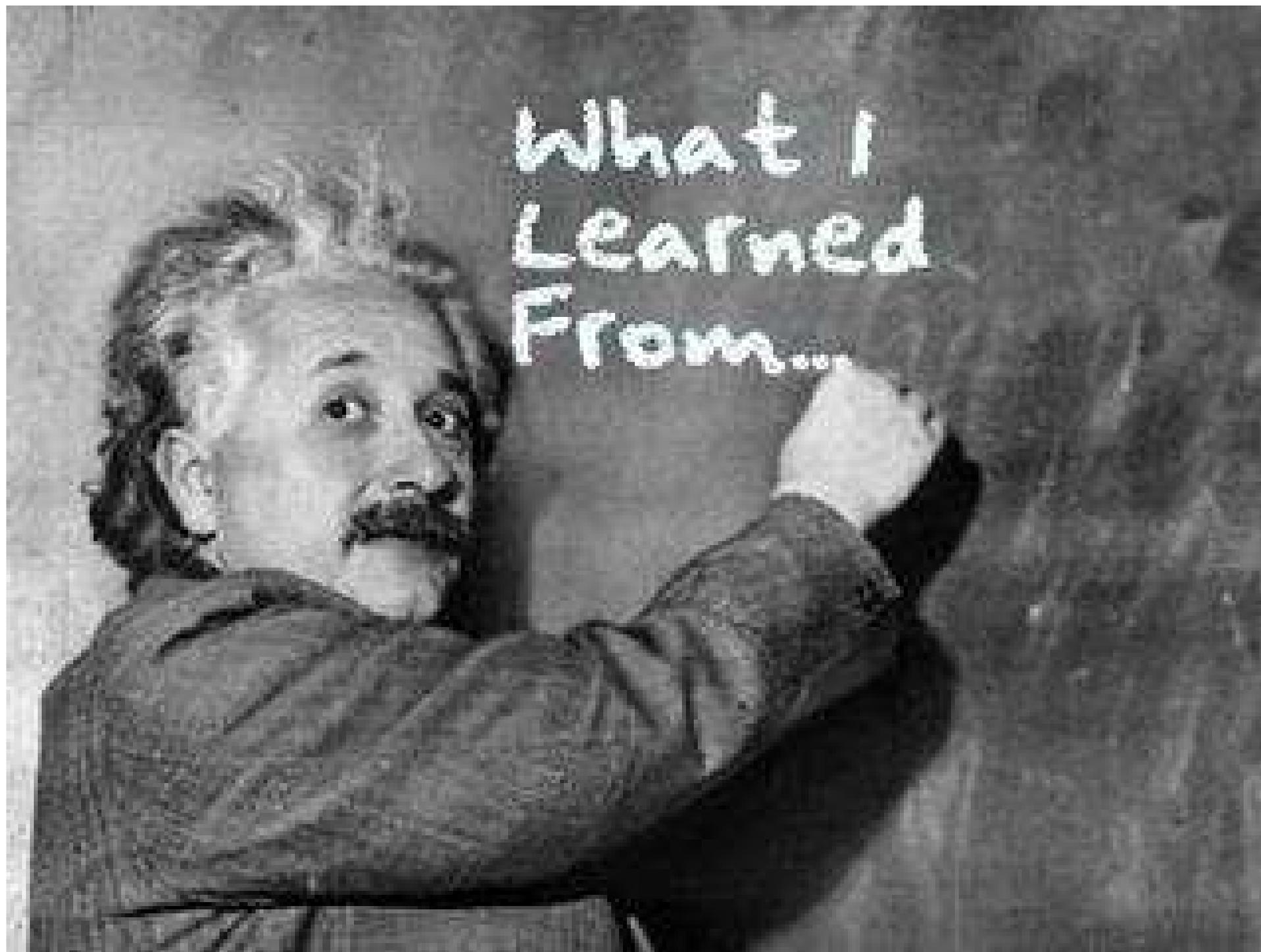


## Second Line Treatment

- Quadruple therapy: PPI+ metronidazole+ amoxicillin+ bismuth.
- Triple therapy: PPI+levofloxacin (moxifloxacin)+amoxicillin.



What I  
Learned  
From...



# *Helicobacter pylori* Infection in Children

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## 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.

# *Helicobacter pylori* Infection in Children

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## Take Home Messages

- 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.

