Helicobacter pylori: Diagnosis, treatment and risks of untreated infection

Klaus Mönkemüller
Department of Gastroenterology, Hepatology und Infectious Diseases
Otto-von-Guericke University, Magdeburg
<table>
<thead>
<tr>
<th><strong>Helicobacter pylori Diagnosis</strong></th>
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<tbody>
<tr>
<td><strong>Invasive</strong></td>
</tr>
<tr>
<td>Rapid urease test</td>
</tr>
<tr>
<td>Histology</td>
</tr>
<tr>
<td>Microbiology</td>
</tr>
<tr>
<td>(FISH, PCR)</td>
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</tbody>
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Helicobacter pylori Diagnosis

Rapid urease test

- Sensitivity / Specificity > 90%
- One biopsy from each antrum & corpus
- Cost effective

Labenz et al. Digestion 1999
Malfertheiner et al. Eur J Gastroenterol Hepatol 1996
Statement:
In patients presenting for endoscopy without pre-treatment, a positive RUT is sufficient to initiate a therapy.
Urea breath test

$^{13}$CO$_2$

$^{13}$C-labeled urea

urease

ammonia

$^{13}$CO$_2$

$^{13}$CO$_2$

Urea blood test
PPI decrease sensitivity of UBT for detection of *H. pylori*

- $^{13}$C-UBT turned negative in 50% of patients after 5 days therapy with 80 mg of Omeprazole
  - Stoschus B et al. Eur J Gastroenterol 1996
- Mechanism: unknown
  - Inhibits *Hp* growth
  - Reduces the concentration of bacteria
  - Decreased urea entrance into bacteria
- Available UBT and stool Ag tests become reliable only 2-6 weeks after stopping antibiotics + PPIs
False negative due to PPI is dependent on PPI

- 179 patients
- PPI x 14 days, then UBT
  - (high dosage citric acid 4 gm)

<table>
<thead>
<tr>
<th>Medication</th>
<th>False negatives</th>
</tr>
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<tbody>
<tr>
<td>Omeprazole 20mg/d</td>
<td>4.1%</td>
</tr>
<tr>
<td>Pantoprazole 40mg/d</td>
<td>2.2%</td>
</tr>
<tr>
<td>Lansoprazole 30mg/d</td>
<td>16.6%</td>
</tr>
<tr>
<td>Esomperazol 40mg/d</td>
<td>13.6%</td>
</tr>
</tbody>
</table>

Levine et al APT 2005
European Multicenter Study to compare various non-invasive methods for the diagnosis of *H. pylori*

Sensitivity

Specificity

Malfertheiner et al. Gut 2001
Question: Which are the non-invasive tests to be used in the test and treat strategy?

**Statement:**

The non-invasive tests that can be used for the test and treat strategy are UBT and the stool antigen tests. Certain kits for serology with high accuracy can also be applied.
Statement:
PPI is a source of false negative diagnostic tests except serology. PPI should be stopped for at least 2 weeks before performing the diagnostic test.

Level of Evidence: 1
Grade of Recommendation: A

Values in percentage

- I agree: 92.9%
- I don’t agree: 7.1%
Helicobacter pylori Diagnosis

Evaluation of eradication

- $^{13}$C-breath test
- Stool antigen-test

Statement:

It is recommended to follow up patients after *H. pylori* eradication with UBT if available. If not available a laboratory-based stool test, preferably using monoclonal antibodies, could be used.
**Maastricht 3-2005**

**First line options**

- **PPI**  
  Clarithromycin  
  2 x Stand.  
  2 x 500 mg  
  (if clarithromycin resistance < 15%)

- **PPI**  
  Clarithromycin  
  2 x Stand.  
  2 x 500 mg  
  (if metronidazole resistance , 40%)

- **Bismuth based Quadruple Therapies**

**Duration of therapy: at least 7 days, max. 14 days**
### Primary clarithromycin resistance in Europe

<table>
<thead>
<tr>
<th>Country</th>
<th>Resistance range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sweden, 1997</td>
<td>2.7</td>
</tr>
<tr>
<td>Finland, 2004</td>
<td>2.0</td>
</tr>
<tr>
<td>U.K., 2001-2004</td>
<td>4.4 - 7</td>
</tr>
<tr>
<td>Ireland, 1996</td>
<td>4.5</td>
</tr>
<tr>
<td>Germany, 1998-2001</td>
<td>2.0 - 4.9</td>
</tr>
<tr>
<td>Belgium, 1992-1997</td>
<td>1.7 - 10.5</td>
</tr>
<tr>
<td>France, 1997-2000</td>
<td>2.0 - 11.0</td>
</tr>
<tr>
<td>Italy, 2000-2003</td>
<td>1.8 - 23.4</td>
</tr>
<tr>
<td>Spain, 1998 - 2000</td>
<td>5.7 - 6.2</td>
</tr>
<tr>
<td>Bulgaria, 2004</td>
<td>11.9</td>
</tr>
</tbody>
</table>
Expected Eradication rates of PPI-CA and PPI-CM according to resistance rate to Clarithromycin (C) and Metronidazole (M)

Megraud F. Current Infectious Disease Reports 2005
Resistance according to underlying disease

Patients not previously treated

Resinet, Professor Manfred Kist, Freiburg, Germany, Dec 2006
Smoking increases the therapeutic failure of *H. pylori* eradication

- Meta-Analysis: 22 Studies, 5538 patients
- OR eradication failure: smoker versus non-smoker: **1.95** (p<0.01)
- Difference of eradication rates: **8.4%**

Maastricht 3-2005

Question: What is the recommended first line treatment?

Statement:
• PPI – clarithromycin amoxicillin or metronidazole therapy remains the recommended first line therapy in populations with less than 15-20% clarithromycin resistance prevalence. In population with less than 40% metronidazole resistance prevalence PPI – clari - metro is preferable.
• Quadruple therapies are alternative first line therapies.
# Efficacy of short and long therapies for *H. pylori* infection

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Duration (days)</th>
<th>Increase in cure rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triple</td>
<td>14 vs 7</td>
<td>9% - 12%</td>
</tr>
<tr>
<td></td>
<td>10 vs 7</td>
<td>3%</td>
</tr>
<tr>
<td></td>
<td>14 vs 10</td>
<td>2%</td>
</tr>
<tr>
<td>Quadruple</td>
<td>10-14 vs 7</td>
<td>6%</td>
</tr>
</tbody>
</table>

*Calvet X et al. APT 2000;14:603-9*
*Fishbach LA et al APT 2004;20:1071-82*
*Ford A. et al. Can J Gastroenterol 2003; 17: 36-40*
CYP2C19 Polymorphisms

Schwab et al Clin Pharmacol Ther 2004
Question: Which one is the second line therapy of choice?

Statement:
• Wismut-based quadruple therapies remain the best second line therapy, if available. If not PPI amoxicillin or tetracyclin and metronidazole are recommended.

Evidence: 2  Grade of Recommendation: B
PPI, Rifabutin and Levofloxacin versus Quadruple Therapy as Second Line Treatment

Wong, Aliment Pharmacol Ther 2003, 17: 553-560
Reserve therapies (1)

1. PPI-AM-Therapy („Englishe Therapy“) (14 days)
   - PPI 2 x SD/Amoxicillin 2x1g/Metronidazol 2x400mg

2. High dose-dual therapy (14 days)
   - PPI (3x SD), Amoxicillin 3x1g

3. Rifabutin-based therapy (7 days)
   - PPI 2 x SD/Amoxicillin 2 x 1g/Rifabutin 2 x 150mg
4. **Bismuth-based quadruple**
   PPI-Standard dosage + Bismutsubcitrat (2 x 240 mg)
   Tetrazyclin (4 x 500 mg) + metronidazol (4 x 500 mg) or
   furazolidone* (2 x 200 mg) x 7 - 14 days

5. **Gyrase inhibitor & Amoxicillin (7 days)**
   PPI 2 x SD/Amoxicillin 2 x 1g/Levofloxacin 1 x 500 mg
   or Moxifloxacin 1 x 400 mg

6. **Rifabutin & gyrase inhibitor (if Penicillin-Allergy) (7 days)**
   PPI 2 x SD/Rifabutin 2 x 150mg/ 1 x 500 mg or
   Moxifloxacin 1 x 400 mg
Statement:
The rescue therapy should be based on antimicrobial susceptibility testing

Level of Evidence: 2c  Grade of Recommendation:  B

Values in percentage
### Development of Peptic Ulcer in NUD Patients

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Eradication Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blum</td>
<td>4.0 %</td>
<td>0.6 %</td>
</tr>
<tr>
<td>Talley</td>
<td>5.0 %</td>
<td>0.2 %</td>
</tr>
<tr>
<td>Hsu</td>
<td>7.5 %</td>
<td>2.5 %</td>
</tr>
<tr>
<td>McColl</td>
<td>2.0 %</td>
<td>0 %</td>
</tr>
</tbody>
</table>

*Cochrane Library 2005*
H. pylori and gastric cancer

Effects on gastric physiology

- Urease
- LPS
- Cytotoxin
- VacA
- CagA

- Hp-Ag
- NO
- ROS
- PMN

- IL-8; IL1β
- T-helper cells
- Macrophages

- Gastrin
- Somatostatin

↓ H+  
↑ Atrophy

El Omar 2000
**H. pylori** infection and gastric cancer: A prospective endoscopy study

- 1526 patients with NUD, DU, GU or gastric hyperplasia (GH)
- Endoscopy: enrollment and every 1-3 years
- No antibiotic treatment
- Mean follow-up: 7.8 years

H. pylori Infection und stomach CA
A prospective endoscopic study
Gastric Histology and cancer in non-ulcer dyspepsia

<table>
<thead>
<tr>
<th>Baseline</th>
<th>N</th>
<th>HP+ with gastric cancer n=36</th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrophy moderate</td>
<td>657</td>
<td>2.7%</td>
<td>1.7 (0.8-3.7)</td>
</tr>
<tr>
<td>Atrophy severe</td>
<td>208</td>
<td>7.2%</td>
<td>4.9 (2.8-19.2)</td>
</tr>
<tr>
<td>Intestinal metaplasia</td>
<td>464</td>
<td>6.5%</td>
<td>6.4 (2.6,16.1)</td>
</tr>
</tbody>
</table>

Impact of *H. pylori* infection on gastric cancer incidence

Follow-up: 9 years

Relative risk of CA: 2.59

Yamagata Arch Int Med 2000
Statement:

*H. pylori* infection is the most common proven risk factor for human non-cardia gastric cancer.
H. pylori, NSAID use, and risk of peptic ulcer disease: Meta-analysis of 5 case control studies

Huang et al, Lancet 2002; 359:14-22
Statement:

*H. pylori* eradication is of value in chronic NSAID users but is insufficient to completely prevent NSAID-related ulcer disease

Level of Evidence: 1b
Grade of Recommendation: A

Values in percentage

I agree | I don't agree
---|---
90.5 | 9.5
Statement:
Patients who are on long-term aspirin who bleed should be tested for *H. pylori*, and if positive receive eradication therapy.

Level of Evidence: 1b   Grade of Recommendation: A
Conclusions

• Best tests for the diagnosis of *H. pylori*: RUT, UBT, antigen stool test
• Triple therapy remains standard eradication strategy
  – Choose regimen based on resistance patterns in your area
  – 14 days increase eradication rates but are not cost-effective
  – Smoking decreases eradication rates
• Rescue therapies (> 2) should be based on susceptibility testing (antibiogram)
• Untreated *H. pylori* infection will lead (varying %) to peptic ulcer, atrophic gastritis, intestinal metaplasia, gastric cancer, etc.