Educational Workshop

EW07: *Helicobacter pylori* susceptibility testing and treatment failure

arranged with EHSG (European *Helicobacter* Study Group)

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Leif Andersen, Copenhagen, DK
Xavier Calvet, Barcelona, ES
Francis Mégraud
Why current treatment fails?

**H. pylori eradication**

Why treatment fails?

Francis Mégraud

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Bordeaux, France

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**Maastricht 2005 Consensus Report**

- First line therapy
  PPI/RBC-Clarithromycin-Amoxicillin or Metronidazole
  (bd) (500 mg bd) (1 g bd) (500 mg bd)

- Second line therapy
  PPI- Bismuth - Tetracycline - Metronidazole
  (bd) (120 mg qd) (500 mg qd) (500 mg td)

- Third line therapy attempt given on a case by case basis
  Malfertheiner et al., Gut 2007;56:772-81

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Why treatment fails?

Because the antibiotic concentration at the site of the infection is below the MBC of the antibiotic against *H. pylori*

MIC surrogate of MBC
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Why current treatment fails?

Why does it occur?
1. The patient does not take the drugs properly (compliance)
2. MBC & MIC are higher than normal because of mutations (resistance)
3. MBC & MIC are higher than normal because the pH is too low (hypersecretors)
4. MBC & MIC are higher than normal because the load of bacteria is very high (inoculum effect)

Why does it occur? (2)

Other possibilities:
• presence of Cag negative strains
• sanctuaries not reached by the antibiotics
• dormant forms not accessible to antibiotics
• impaired host mucosal immunity

H. pylori eradication according to compliance assessed by Medication Event Monitoring System containers

Bad compliers (<85% dose) represented 11.5% of the patients

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Why current treatment fails?

How to improve compliance of current therapies

• explain compliance to the patient
• add probiotics?

Metaanalysis of the effect of supplementation of Triple Therapy by probiotics

Tong et al. APT 2007;25:155-68

Genes concerned by point mutations leading to antibiotic resistance in *H. pylori*

<table>
<thead>
<tr>
<th>Antibiotic group</th>
<th>Genes concerned</th>
<th>Frequency of resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macrolides</td>
<td>23S rRNA</td>
<td>0-25%</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>rdxA, frxA</td>
<td>10-90%</td>
</tr>
<tr>
<td>Quinolones</td>
<td>gyrA</td>
<td>0-20%</td>
</tr>
<tr>
<td>Rifamycins</td>
<td>rpoB</td>
<td>0-5%</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>pbp-1A</td>
<td>few cases described</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>16S rRNA</td>
<td>few cases described</td>
</tr>
</tbody>
</table>
Francis Mégraud  
Why current treatment fails?

**Resistance of *H. pylori* to clarithromycin in Europe**

No. of isolates tested: 1305 (mean No./Center = 59, range: 19-104)


**Resistance of *H. pylori* to metronidazole in Europe**

No. of isolates tested: 1305 (mean No./Center = 59, range: 19-104)


**Eradication of *H. pylori* in 20 clinical trials (1999-2003) using PPI-clarithromycin-amoxicillin according to clarithromycin susceptibility**

Mantel Haenszel pooled OR=24.5 [95 CI 17.2-35].  
70% decrease in *H. pylori* eradication if the strain is Clari R

Mégraud F., Gut 2004;53:1374-84
Francis Mégraud

Why current treatment fails?

Eradication of *H. pylori* in 8 clinical trials (1999-2003) using PPI-clarithromycin-metronidazole according to susceptibility to both antibiotics

![Graph showing eradication rates](image)

Mantel Haenszel pooled OR=11.3 [95% CI 5.7-22.3]
25% decrease in *H. pylori* eradication if the strain is Metro R

Mégraud F., Gut 2004;53:1374-84

Eradication of *H. pylori* in 6 clinical trials (1999-2003) using PPI-amoxicillin-metronidazole according to metronidazole susceptibility

![Graph showing eradication rates](image)

25% decrease in *H. pylori* eradication if the strain is Metro R

Mégraud F., Gut 2004;53:1374-84

**MIC of various antibiotics against susceptible *Helicobacter pylori* according to pH**

<table>
<thead>
<tr>
<th>Agent</th>
<th>pH 7.5</th>
<th>pH 6.0</th>
<th>pH 5.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin</td>
<td>0.03</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>0.06</td>
<td>0.25</td>
<td>0.5</td>
</tr>
<tr>
<td>Cephalexin</td>
<td>2</td>
<td>16</td>
<td>32</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>0.06</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>0.03</td>
<td>0.06</td>
<td>0.25</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>0.12</td>
<td>0.5</td>
<td>2</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>0.12</td>
<td>0.25</td>
<td>0.5</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Bismuth subcitrate</td>
<td>16</td>
<td>8</td>
<td>-</td>
</tr>
</tbody>
</table>

Goodwin 1992, Mégraud 2002
Francis Mégraud
Why current treatment fails?

**Low gastric pH**
- Existence of acid “hypersecretors”
  - basal acid output > 15 mmol/h
  - normal gastrin level
  - Hirschowitz 1996
- Existence of extensive metabolizers of PPI
  - by cytochrome P450 isozyme CYP2C19.
  - mean 24 h intragastric pH value of subjects treated with PPI:
    - 4.5 extensive metabolizers
    - 5.5 poor metabolizers
  - Furuta 2001

**Relationship between pre-treatment UBT values and efficacy of H. pylori eradication**
- 108 patients (DU-NUD)
- PPI-amoxi-clari (or tini) 1 week
- 82% eradication
- 67% eradication
- 17% eradication
- Median DOB value 15.7 (success) vs. 21.6 (failure)
  - Perri et al. Ital J Gastroenterol Hepatol 1998;30:146-50

**Relationship between pre-treatment bacterial density at histology and H. pylori eradication**
- 127 patients (DU)
- Bismuth based triple therapy 2 weeks
- 88.3% eradication
- 83.8% eradication
- 74.2% eradication
- 68% eradication
- 50% eradication
  - Shen et al. Gastrointest Endosc 1996;44:833-8
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Why current treatment fails?

Meta-analysis of the impact of the CagA status on *H. pylori* eradication by Triple Therapy

Suzuki et al. APT 2006;24:273-80

OR= 20 (95% CI 1.6-2.4)

Arguments for the role of intracellular *H. pylori* in evading treatment

- *H. pylori* antigens (HSP60) can be expressed on epithelial cells *in vivo* (Engstrand et al. 1997)
- *H. pylori* can survive in PMN (Andersen 1993) and in epithelial cells (Wilkinson 1998)
- *H. pylori* can repopulate the extracellular environment from intravacuolar bacteria (Amieva 2002)

Internalization

Lozniewski 2003
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Why current treatment fails?

Conclusion

• Susceptibility testing is now necessary to obtain optimal eradication rate when prevalence of resistance reaches 15-20%, for clarithromycin and levofloxacin

• Explanation of the treatment adverse events must be given to the patient
Helicobacter pylori:
How to perform susceptibility testing?

A. M. Hirschl
Department of Clinical Microbiology
Institute of Hygiene and Medical Microbiology
Medical University Vienna

In vitro susceptibility / resistance of H. pylori against antibacterial agents

• Wild type susceptibility
  – aminoglycosides
  – ß-lactams (exc. cefsulodin)
  – chloramphenicol
  – fluoroquinolones
  – fosfomycin
  – linezolid
  – macrolides
  – nitrofurantoin
  – nitroimidazoles
  – rifamycines
  – tetracyclines
  – bismuth salts

• Intrinsic resistance
  – cefsulodin
  – glycopeptides
  – nalidixic acid
  – polymyxin
  – sulfonamides
  – trimethoprim

Which antibiotics should be tested?

• Clarithromycin
• Levofoxacin or Ciprofloxacin
• Amoxicillin
• Rifampicin
• Tetracycline
• (Metronidazole)
How to perform susceptibility testing?

Phenotypic, culture based methods

- Antibiotic dilution tests
  - agar
  - breakpoint susceptibility testing
  - (broth)
- Antibiotic diffusion tests
  - disc
  - E-test

Conditions of H. pylori susceptibility testing

- Medium: Mueller Hinton agar + 5% sheep blood (CLSI) or 10% horse blood (EHSG)
- Inoculum: $10^7-10^8$ cfu/ml (McFarland 2; CLSI) or $5.10^8-10^9$ cfu/ml (McFarland 3-4; EHSG) prepared from 2-3 day culture
- Incubation: 35-37 °C, microaerobic atmosphere for 3 days

Interpretative standards for H. pylori

<table>
<thead>
<tr>
<th>Method</th>
<th>Agent</th>
<th>S</th>
<th>I</th>
<th>R</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agar-dilution (CLSI)</td>
<td>Clarithromycin</td>
<td>≤ 0.25</td>
<td>0.5</td>
<td>≥ 1</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>≤ 1</td>
<td>-</td>
<td>-</td>
<td>&gt; 1</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>≤ 8</td>
<td>-</td>
<td>-</td>
<td>&gt; 8</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>≤ 2</td>
<td>-</td>
<td>-</td>
<td>&gt; 2</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>≤ 1</td>
<td>-</td>
<td>-</td>
<td>&gt; 1</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>≤ 1</td>
<td>-</td>
<td>-</td>
<td>&gt; 1</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>≤ 4</td>
<td>-</td>
<td>-</td>
<td>&gt; 4</td>
</tr>
</tbody>
</table>
Alexander Hirschl

How to perform susceptibility testing?

Validation of a disc diffusion method for macrolide susceptibility testing of H. pylori

- MH-agar with 10% horse blood
- inoculated with a 2 day old culture (10^6 cfu/ml)
- erythromycin and clarithromycin discs (15 µg)
- incubated for 72 h at 37°C (microaerobic cond.)
- 100% concordance between erythromycin and clarithromycin susceptibility
- better separation between resistant and susceptible populations by testing erythromycin
- breakpoint: 17 mm for erythromycin

Grignon et al, Microb Drug Res 2002

Frequency distribution of inhibition zone diameter (1 µg disc) and MIC (E-test) for levofloxacin

Comparison of E-test and agar-dilution results for testing the susceptibility of 11 H. pylori strains in four different laboratories

<table>
<thead>
<tr>
<th>Antimicrobial Agent</th>
<th>Percent agreement</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>± 1 log2 dilution</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>82,0</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>85,0</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>57,5</td>
</tr>
</tbody>
</table>

Glupczynski et al, Eur J Clin Microbiol Inf Dis 2002
Alexander Hirschl  
How to perform susceptibility testing?

Comparison of the inter-test variability for categorizing the susceptibility of amoxicillin, clarithromycin and metronidazole using the E-test and agar dilution

<table>
<thead>
<tr>
<th>Antimicrobial Agent</th>
<th>Equivalent categorization %</th>
<th>Major error¹ %</th>
<th>Very major error %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin</td>
<td>100</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>100</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>68.5</td>
<td>32.5</td>
<td>0</td>
</tr>
</tbody>
</table>

¹susceptible by AD, resistant by E-test


H. pylori resistance

- Chromosomal point mutations
- Selected by the administration of antibiotics
- Only vertically transmitted to the immediate offspring
- Horizontal (plasmid mediated) transmission not yet described

Genes with point mutations leading to H. pylori resistance

<table>
<thead>
<tr>
<th>Agent</th>
<th>Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macrolides</td>
<td>23S rRNA</td>
</tr>
<tr>
<td>Amoxicillin</td>
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<td>Rifamycines</td>
<td>rpoB</td>
</tr>
</tbody>
</table>
Alexander Hirschl

How to perform susceptibility testing?

The impact of molecular methods of H. pylori susceptibility testing

- Mainly developed for the detection of macrolide resistance
- Rapid and accurate: same day result
- Culture independent: performed on biopsy specimens or samples taken in the course of non-invasive diagnostic procedures (stool, saliva)
- More sensitive than phenotypic methods in detecting resistant subpopulations
- Knowledge of the precise mechanism required (failure to recognize the new)
- Geographical differences in the location of the mutations must also be considered

Mechanisms of H. pylori resistance against macrolides

![Diagram of 23S rDNA and Chromosome]

Rate of detection of specific 23S rDNA mutations among 129 strains containing non wild-type 23S rDNA sequences from 6 laboratories (PCR line probe assay)

<table>
<thead>
<tr>
<th>Number of strains</th>
<th>A2143G</th>
<th>A2142G</th>
<th>A2142C</th>
<th>multiple*</th>
</tr>
</thead>
<tbody>
<tr>
<td>57</td>
<td>42</td>
<td>2</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>44.1%</td>
<td>32.6%</td>
<td>2.6%</td>
<td>21.7%</td>
<td></td>
</tr>
</tbody>
</table>

* various combinations of wild type, A2142G, A2142C and A2143G

Van Doorn et al. Antimicrobial Agent Chemother 2001
Detection of specific 23S rDNA mutants among Clarithromycin resistant H. pylori strains

- Europe: predominately A → G transition in positions 2142 or 2143
- Korea (33%), Thailand (>90%) and Bangladesh (100%): T → C transition in position 2182

Molecular methods for the detection of point mutations associated with clarithromycin resistance in H. pylori

- PCR-restriction fragment length polymorphism
- PCR oligonucleotide ligation assay
- DNA-enzyme immunoassays
- PCR line probe assay
- PCR preferential homoduplex formation assay
- DNA sequencing (conventional and pyrosequencing)
- Fluorescent in situ hybridization
- Real time PCR + hybrid thermal analysis

Fluorescence in situ hybridisation (FISH)

- Target: 16S rRNA, 23S rRNA
- Gastric biopsies (native or paraffin-embedded)
- Nucleic acid preparation not required
- Not prone to inhibition
- Visualization of bacteria (incl. coccoid forms) and semiquantitative recording of bacterial density
- Quick (1-3h)
- Observer dependent results
- H. pylori Combi Kit, BACTfish™ technology, (Inzinta Trading Co.)
How to perform susceptibility testing?

Principle of FISH-technology

Detection of *H. pylori* within gastric biopsy sections by whole cell hybridization with fluorescence labeled oligonucleotides

- Detection of *H. pylori* with green fluorescent probe (16S rRNA)
- Detection of clarithromycin resistant *H. pylori* with a mixture of red fluorescent probes (23S rRNA)
- Detection of clarithromycin sensitive and resistant *H. pylori* by simultaneous application of the probes

Real time PCR – specimen collection, delivery and DNA extraction

- Specimens: biopsies, string test, gastric juice, oro-gastric brush samples, stool
- Transport media or preservatives should not be used
- Samples can be stored at ambient temperature for 4h, at 4°C for 24h and indefinitely at ≤ 20°C
- Repeated freezing and thawing should be avoided
- DNA extraction: QIAmpDNA minikit or QIAmpDNA stool minikit
- DNA extracts may be stored at 4°C
Alexander Hirschl
How to perform susceptibility testing?

Detection principle: Hybridization Probes

Sequence specific detection of DNA in real-time PCR

Detection Principle: Bi-Probe

Real time PCR for the detection of mutations in the 23S rRNA gene of H. pylori

- Amplification of a 121 bp fragment of the 23S-rRNA gene including the sites of possible mutations
- Detection of susceptible wild type or mutations with a wild type specific biprobe by melting curve analysis
  - Heating to 95°C: denaturation of the PCR product
  - Cooling down to 35°C: probe binding and start of fluorescence
  - Stepwise heating
  - Probe dissociation and decline of fluorescence
Alexander Hirschl
How to perform susceptibility testing?

Melting curves of CLA-susceptible and resistant H. pylori strains

Real time PCR for the detection of mutations in the 23S rRNA gene of H. pylori

- Gibson et al, J Clin Microbiol 1999
  - biprobe, 100 strains
  - SS: 97%; SP: 100%
- Matsumura et al, J Clin Microbiol 2001
  - biprobe, 84 HP-positive biopsy specimens
  - SS and SP: not calculated
- Chisholm et al, J Clin Microbiol 2001
  - biprobe, 56 HP-positive biopsy specimens
  - SS and SP: not calculated
- Oleastro et al, J Clin Microbiol 2003
  - biprobe, 55 HP-positive biopsy specimens
  - SS: 98%; SP: 94%
- Lascols et al, J Clin Microbiol 2003
  - biprobe, 55 HP-positive biopsy specimens
  - SS: 91%; SP: 100%

Comparison of clarithromycin resistance testing by culture and E-test and real time PCR with melting point analysis

<table>
<thead>
<tr>
<th>E-test result (total)</th>
<th>n</th>
<th>PCR-susceptibility pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>biopsy</td>
</tr>
<tr>
<td>Susceptible (34)</td>
<td>33</td>
<td>S</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>S</td>
</tr>
<tr>
<td>Resistant (11)</td>
<td>6</td>
<td>R</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>R+S</td>
</tr>
<tr>
<td></td>
<td>2*</td>
<td>S</td>
</tr>
</tbody>
</table>

* A 2142/2143G

A 2142/2143G

Schabereither-Gurtner et al, J Clin Microbiol 2004
When to perform susceptibility testing?

Leif Percival Andersen, MD
Copenhagen University Hospital
Denmark.

Susceptibility testing

- Susceptibility testing tell us what concentration of a compound (drug) is needed to inhibit the growth of the bacteria or kill them when it comes in direct and close contact with the bacteria.

- It does usually not distinguish between inhibition and killing.

- It does not tell anything about the fate of a compound (drug) in vivo.

- It does not tell anything about what fraction (concentration) of a compound (drug) that will come in contact with the bacteria in vivo.
Leif Andersen
When to perform susceptibility testing?

Susceptibility of *H. pylori* to antibiotics.

- *H. pylori* is almost always susceptible to all antibiotics except
- imidazoles (metronidazole): 30-50% resistance and
- macrolides (clarithromycin): 5-30% resistance.

Susceptibility of *H. pylori* to non-antibiotics.

- Therapeutic concentrations of PPI do not have any direct effect on *H. pylori*.
- Bismuth compounds in therapeutic concentrations inhibit the growth of *H. pylori* and revert metronidazole resistance.
- Antidepressive and antimalaria drugs inhibit or kill *H. pylori*.
- Natural food compounds (astaxanthin, green tea, broccoli etc.) may inhibit the growth of *H. pylori*.

Problems leading to treatment failure of *H. pylori* infections.

- The same standard treatment is used time after time without effect.
- *H. pylori* is susceptible to all antibiotics but no combination is effective for eradicating the bacteria.
- *H. pylori* can be seen by microscopy but can not be cultured. This is occasionally seen after treatment.
Leif Andersen

When to perform susceptibility testing?

Causes of treatment failure.

- Antibacterial resistance to the drugs used.
- Patients compliance to the treatment.
- Drugs do not reach the bacteria.
- Drugs are degenarated or inactivated.
- *H. pylori* is in a protected form (coccoid form or biofilm producing).

When should susceptibility testing be done?

- Ideally: before treatment is initiated to
  - be able to choose correct antibiotics
  - be able to ovoid antibiotics without effect
  - be able to ovoid induction of resistance in the normal flora (skin, gut etc.) to antibiotics without effect on *H. pylori*.

When should susceptibility testing be done?

- After treatment failure after test and treat strategy:
  - probably caused by bacterial resistance to antibiotics
  - susceptibility testing should be done before re-treatment
  - antimicrobial treatment should be changed
  - the opportunity to culture *H. pylori* and make susceptibility testing may be missed in some cases
When should susceptibility testing be done?

- After any treatment failure:
  - probably caused by bacterial resistance to antibiotics
  - susceptibility testing should be done before re-treatment
  - antimicrobial treatment should be changed
  - the opportunity to culture *H. pylori* and make susceptibility testing may be missed in some cases

When should susceptibility testing be done?

- To avoid the increased bacterial resistance to antibiotics, not only in *H. pylori* but also the normal flora (skin, gut etc.) there is an increased need for rational chemotherapy where only active antibiotics are used based on susceptibility testing of the bacteria.

What else should be done?

- Investigate the fate of the drugs systemically and in the stomach
  - are they broken down and inactive or are they still active when they reach *H. pylori*
  - are the drugs able to reach the bacteria and affect them (coccoid form, biofilm)
  - are these properties general or individual for the drugs, the strains and the patients
Leif Andersen
When to perform susceptibility testing?

What else should be done?

• Investigate new antibiotics and other compounds for their antibacterial effect on *H. pylori*.
Xavier Calvet
What will the management of H. pylori infection be in the future?

What will the management of *H. pylori* infection be in the future?

Xavier Calvet. Hospital de Sabadell. CIBER ehd (Barcelona, ES). April 2008

- Where we are now and what do we need
- What will we have in the near future
- Long term expectatives…
Current recommendations

First line:
Standard triple therapy
- PPI standard dose /12h.
- Clarithromycin 500 mg /12h.
- Amoxicillin 1 g /12h. or Metro 500/12h
- 7 to 14 days.
  Quadruple as alternative.

Malfertheiner, P Megraud, F Gut 2007;56;772-781;
Chei, Am J Gastro 2007

Rescue therapy
1. Bismuth-based quadruple therapy.
2. PPI, amoxicillin or tetracycline + metronidazole.
3. based on antimicrobial susceptibility testing.

Malfertheiner, P Megraud, F Gut 2007;56;772-781;
Chei, Am J Gastro 2007
First line treatment: Triple

Triple: Irregular results

Different resistance rates:
• Finland 2%
• England 8-12%
• Belgium 17%
• Italy 17%

Main factors explaining irregular results

- Antibiotic resistance
- Adherence
Xavier Calvet
What will the management of H. pylori infection be in the future?

**Resistances’ evolution**

- Clarithromycin: stable or slightly increase?
- Metronidazole: 30%

Zulio, APT 2007, Runette UEGW 2007, Kivistö APT 2004

**Effect of antibiotic resistance on triple therapy effectiveness**

- Sensitive
- Resistant


**Adherence to antibiotics**

- Adherence rates
- + Affordability
- + Complexity
- + Presentation

Xavier Calvet
What will the management of H. pylori infection be in the future?

First line treatment: Quadruple

Triple vs. Quadruple therapy

<table>
<thead>
<tr>
<th>Study</th>
<th>(95% CI Random)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calvet</td>
<td></td>
</tr>
<tr>
<td>Gomollon</td>
<td></td>
</tr>
<tr>
<td>Katelaris</td>
<td></td>
</tr>
<tr>
<td>Laine</td>
<td></td>
</tr>
<tr>
<td>Mantzaris</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
</tr>
<tr>
<td>.1</td>
<td>.2</td>
</tr>
<tr>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Favours quadruple</td>
<td>Favours triple</td>
</tr>
</tbody>
</table>

Cure rate: 80% vs. 79% triple

Claxton Clin Therap 2001

Quadruple therapy

- Tetracycline
  500 mg /8h. OR /6h.
- Metronidazole
  500 mg /8h.
- Bismuth / 8h. OR /6h.
- PPI /12h.
- 7 to 14 days

Expected adherence to 6-h therapy ≈ 50%

Gené, APT 2003
Xavier Calvet
What will the management of H. pylori infection be in the future?

First line:
Near future changes
• Improving triple
• Sequential
• Easiest quadruple
• Levo first-line?

Improving triple

Increasing the length of treatment
• At least 7 days (Maastricht II)
• 14-day treatment / 7-day acceptable if good local results (Maastricht III)

Xavier Calvet
What will the management of H. pylori infection be in the future?

**Increasing PPI dosage**
- od PPI ↓effective than bd PPI in triple therapy
- 10%- 20% of GERD patients show insufficient acid inhibition on twice-daily PPI
- Europe: > 80% Extensive (rapid) Metabolizers (EM) of PPIs
- Triple therapy: EM: eradication rates vs. Poor Metabolizers (p<0.0001)


**Clinical studies**

<table>
<thead>
<tr>
<th>% Cure rates</th>
<th>standard dose</th>
<th>high dose</th>
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</thead>
<tbody>
<tr>
<td>100</td>
<td>90</td>
<td>80</td>
</tr>
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<td>90</td>
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</tr>
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</table>

RR 1.09, 1.01-1.17

Villoria, AEG 2008

**Easy treatments?**
What will the management of H. pylori infection be in the future?

Barriers to treatment

- Time to explain
- Prescribing the components of treatment separately

McNulty Fam Pract 2006

Levo first?
Xavier Calvet

What will the management of H. pylori infection be in the future?

Levofloxacin-based triple therapy

![Graph showing ITT cure rate]

- High primary resistance rates:
  - Belgium 19%
  - Italy 17%

Sequential treatment

Sequential treatment (10 days)

1. PPI/12h
   - amoxicillin 1g/12h
   - 5 days

2. PPI/12h
   - metronidazole 500 mg/12h
   - clarithromycin 500 mg/12h
   - 5 days
Xavier Calvet
What will the management of H. pylori infection be in the future?

Sequential treatment

- More effective than 7 (1,2,3) and 10 days (4) of triple therapy
- Not affected by risk factors of triple therapy failure (1,2,4)

1) De Francesco, V. Dig Liver Dis 2004
2) Zullo, A. Aliment Pharmacol Ther 2003
3) Francavilla, R. Gastroenterology 2005
4) De Francesco, V. Aliment Pharmacol Ther 2004

Sequential therapy, cure rates

<table>
<thead>
<tr>
<th>Author</th>
<th>year</th>
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<td>Vaira</td>
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<td>Sanchez-Delgado</td>
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Rescue therapy:
Swicht to levofloxacin based triple therapy
Xavier Calvet  
What will the management of H. pylori infection be in the future?

Levofloxacin as rescue treatment

3 Meta-analysis
- Levo (triple) > quadruple therapy
- 10 days > 7 days (88% vs. 78%, p < 0.05)
- 500 mg /12 h > 250 (87% vs. 82%, ns)
- Less side effects

Saad et al DOW 2005

Conclusion
- Maintain triple therapy if good results; 10-14 days & ↑dose PPI could improve cure rates.
- Switch to alternatives if poor local results:
  a) Sequential
  b) Levofloxacin-based triple

Future needs
- Validation of alternative schedules
- Combined drug pills / compliance pack
- New treatments
- Vaccine??