PATHOGENESIS AND CURRENT TREATMENT OF H. PYLORI INFECTION

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Helicobacter Pylori

- Discovery revolutionised the treatment of duodenal and gastric ulcers.
- Since 1994, it has classified as a GROUP 1 (Definite) human carcinogen.
- Earned them the Nobel Prize for Medicine in 2005.
- Formerly known as *Campylobacter pyloridis*
Description

• Gram-negative spiral bacillus

• Fastidious in terms of growth requirements
  : strictly micro-aerophilic
  : require CO2 for growth
  : on charcoal medium

• Has a tuft of sheathed unipolar flagella; specially adapted to colonise mucous membranes
• Hallmark of the species is production of urease enzyme
  - urease breaks urea down to C02+NH3
  - amonia is a strong base
  - process helps *H. pylori* survive strongly acidic stomach conditions

• Very fragile (a point of importance when referring samples to the lab)
Site of infection

- Highly adapted organism that lives only on gastric mucosa
- Gastric antrum is the most favoured site
- Present in the mucus that overlies the mucosa
The prevalence of H. pylori is decreasing in industrialized countries.
Transmission

• Oral ingestion of bacterium within families (esp children) person-person contact faecal-oral transmission ?role of waterborne transmission

• Usually contracted in the first 2 years of life
Gastric-biopsy specimen showing *Helicobacter pylori* adhering to gastric epithelium and underlying inflammation.
Course of infection

• After several days incubation period, patients suffer mild attack of acute gastritis:
  - abdominal pain
  - nausea
  - flatulence
  - bad breath

• Symptoms last about 2/52 but hypochlorhydria can last up to one year
The good, the bad and the ugly....
H. pylori
H. pylori infection directly associated with

- **PUD**
  - lifetime risk 3% in US, 25% Japan
  - eradication provides long-term cure

- **Gastric carcinoma**
  - strong evidence of increased risk 0.1-3%
  - unclear whether eradication reduces the risk of gastric cancer

- **MALT lymphoma**
  - 72% → 98% of MALT lymphoma infected with H. pylori
**H. pylori Infection & Gastroduodenal Disease**

**Chronic H. pylori Infection**

- **15%**
  - Antral predominant Gastritis
    - Acid, little or no atrophy
    - Low risk of gastric ca

- **80-85%**
  - Mild Mixed Gastritis
    - Normal Acid

- **~1%**
  - Corpus predominant Gastritis
    - MAG + Hypochlorhydria
    - High risk of gastric ca

**DU disease**

**No significant disease**

**Gastric Ca**

? Bacterial ? Environment ? Host
The outcome of infection by *H. pylori* reflects an interaction between:

- Strain virulence
- Environmental factors
- Host genotype
*Helicobacter pylori*

- **Spiral-shaped** Gram-negative, oxidase and catalase-positive motile bacterium with 4-6 flagella

- **Microaerophilic**, i.e. it requires oxygen but at lower levels than those contained in the atmosphere

- With its flagella and its spiral shape, the bacterium drills into the mucus layer of the stomach, and can either be found suspended in the gastric mucosa or attached to epithelial cells
Pathogenesis

- *H. pylori* is found only on gastric epithelium where the organisms tend to cluster around the junctions between cells and virtually never penetrate the cells themselves.
- *H. pylori* is able to survive in the gastric environment which is hostile to growth of most bacteria.
Pathogenesis

- Urease production essential for survival – urease hydrolyses urea into carbon dioxide & ammonia permitting survival in acidic milieu.

- Motility essential for colonisation – HP flagella have adapted to gastric niche.

- Vacuolating cytotoxin (VacA) – expressed by majority of strains of HP, appears to increase bacterial fitness.

- Huge variation in VacA strains.
Host response to infection

- *H. pylori* attaches to gastric epithelial cells triggering host inflammatory response
- *H. pylori* bind to class II MHC molecules on surface of gastric epithelial cells inducing apoptosis
- HP urease & porins may contribute to extravasation & chemotaxis of neutrophils
- HP infected patients gastric epithelium have enhanced levels of IL-1β, IL-2, IL-6, IL-8, TNFα
- IL-8 appears to have a central role
Host response to infection

- Marked systemic & mucosal humoral response – antibodies do not lead to eradication of the infection but may contribute to tissue damage

- Th1 response predominates and Th1 cytokines promote gastritis – may occur due to increased IL-8 production
The proteins encoded by these genes assemble to form a complex type IV secretion apparatus capable of delivering CagA from the bacterium into host cells.

Translocation of CagA into gastric epithelial cells

Phosphorylation of CagA by host-cell kinases c-Src and Lyn

Binding to and activation of cellular phosphatase SHP-2

Growth factor–like response in host cell, cytoskeletal rearrangements
H. pylori cag+ strains can induce or prevent gastric epithelial-cell apoptosis.
Pathogenesis

- **H. pylori Genome Changes** continuously
- **Hop Proteins, Adhesins**
- **Ure 1, pH Gated urea channel**
- **Bab A adhesin**, **Binds fucosylated Lewis B Blood group antigen**
- **Vac A Gene Variants**, **More severe disease**
- **Cag Pathogenicity Island**, **translocates CagA into host cell**, phosphorylated, **Binds SHP-2 TP → Growth factor-like Cellular response and Cytokine production by Host cell**
**Diagnosis of the infection**

<table>
<thead>
<tr>
<th>Invasive tests</th>
<th>Non invasive tests</th>
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<tbody>
<tr>
<td>✓ Histology.</td>
<td>✓ Urea breath test.</td>
</tr>
<tr>
<td>✓ Rapid Urease test.</td>
<td>✓ Stool antigen test.</td>
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<tr>
<td>✓ Culture.</td>
<td>✓ Serology.</td>
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<tr>
<td>✓ Molecular tests.</td>
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<tr>
<td>✓ “Advanced ” endoscopy.</td>
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Histology (sensitivity and specificity > 95%)

✔ Old, classic method ("gold standard").

✔ Classification of gastritis and detection of pre-cancerous lesions

✔ Increased sensitivity from examination of more samples taken from different parts of the stomach.

Lee et al. Helicobacter 2012.
Rapid Urease test (CLO test)

✓ Indirect method of detection.

✓ Quick, cheap and reliable.

✓ Sensitivity: 95%.

✓ Specificity: 90%.

✓ Increased sensitivity with 2 samples from antrum and corpus.

✓ Newer test with rapid results (Pyloritek: 1h, Ultrafast RUT: 5min)

Moon et al, Clin Endosc 2012, Vaira, Aliment Pharmacol Ther 2010
Culture of the H. pylori

✓ Expensive, time-consuming, not widely available technique.

✓ Specificity: 100%.

✓ Sensitivity: till 90%

✓ Main indication: Detect sensitivity in antibiotics after two unsuccessful treatments.
The endoscopy is mandatory...

Age > 45 years

Alarm symptoms

Otherwise...

Test and Treat
Urea Breath Test

Sensitivity and Specificity > 95%.

✓ Sensitivity: ↓ recent administration of PPIs, Bi or Antibiotics
✓ Off PPIs: for at least 2 weeks.
Stool antigen test

✓ Easy.

✓ Based on ELISA.

✓ Popular and useful in children.

✓ Needs to be stored in -20° C.

✓ *Maastricht IV*: Use only monoclonal antibodies.
Serological methods

✓ It is the oldest non invasive method.
✓ Cheap and widely available.
✓ IgG & IgA antibodies.
✓ It can be used in epidemiological studies, in active bleeding, recent use of antibiotics or PPIs, or diffuse gastric atrophy or metaplasia.
✓ Diagnostic accuracy: almost 90%.
The only good H. pylori is the dead H. pylori.
Maastricht IV Consensus Report

- PUD
- Atrophic gastritis
- MALT lymphoma
- First degree relatives of pts with gastric Ca
- NUD
- Long term use of NSAIDS/Aspirin or PPIs
- IDA, ITP
- Strong patient’s wish for treatment
What is the ideal therapeutic schedule

✓ Efficacy: $\geq 90\%$

✓ Serious side effects: $< 5\%$

✓ Achieves compliance

✓ Cheap
The problem of resistance

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<tr>
<th>Europe</th>
<th>Greece</th>
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<tr>
<td>CLA</td>
<td>CLA</td>
</tr>
<tr>
<td>17.5%</td>
<td>25-30%</td>
</tr>
<tr>
<td>(N:7.7%, C&amp;W:18.7%, S:21.5%)</td>
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<tr>
<td>LEV</td>
<td>LEV</td>
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<tr>
<td>14%</td>
<td>10%</td>
</tr>
<tr>
<td>(N:7.7%, C&amp;W:18.6%, S:13.1%)</td>
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<tr>
<td>MET</td>
<td>MET</td>
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<tr>
<td>35%</td>
<td>45%</td>
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<tr>
<td>PIFA</td>
<td></td>
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<tr>
<td>1.1%</td>
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<tr>
<td>AMO</td>
<td>AMO</td>
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<tr>
<td>0.7%</td>
<td>0-1%</td>
</tr>
<tr>
<td>TET</td>
<td>TET</td>
</tr>
<tr>
<td>0.9%</td>
<td>0-1%</td>
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Megraud, GUT 2013
Available therapeutic regimens
Classic Triple Regimen

- PPI b.d. + clarithromycin 500mg b.d.
  - +
- amoxicillin 1000mg b.d. or metronidazole 400mg BD minimum of 7 days

- Still popular.
- 2 large studies from Korea: 85 & 90%,
  - WJG 2012, J Clin Gastroenterol 2013
- Recent studies from Mexico, Spain, Greece, Japan, India: 49-78%.
What can we do to increase efficacy?

✓ Quadruple regimens without bismuth
  - sequential
  - concomitant
  - hybrid

✓ Quadruple regimens with bismuth

✓ Use of fluoroquinolones (Levofloxacin)
Quadraple treatment without Bismuth

Sequential

PPI + AMO for 5 days
then
PPI + KLA + MET for 5 days
(all b.i.d.)

Eradication rate in Greece: 90%
Sequential vs. Classic triple

5000 patients

Eradication rate: 86% vs. 75% p<0.001

Concomitant

PPI + AMO + KLA + MET for 10-14 days
(all b.i.d.)

Eradication rate in Greece: 92%
Efficacy of concomitant treatment in the Greek population

Georgopoulos SD, et al. Helicobacter 2013; 459
Concomitant vs. Classic triple

✓ Greece: 10 days
  90.5% vs. 74% ITT (93% vs. 78.5% PP)
✓ Korea: 5 days
  91% vs. 86% PP
✓ Japan: 7 days
  95% vs. 68% ITT (98% vs. 73% PP)

Georgopoulos SD, et al. JCG 2013; 228
Kim SY, et al. JCG 2013; 21
Yanai, WJ GP 2012; 1
Concomitant vs. Sequential

- Better compliance
- Slightly better efficacy
- Higher success rate of concomitant in case of double resistance: 50-100% vs. 0-60%

O’Connor A, et al. Helicobacter 2013; S1: 58
Georgopoulos SD, et al. Gastro 2013; 1497
Quadruple treatment without Bismuth

Hybrid

PPI + AMO for 7 days
and
PPI + AMO + KLA + MET for 7 days
(all b.i.d.)

Eradication rate in Greece: 92%
Comparative studies with Hybrid treatment

✓ Iran: Hybrid vs. Sequential
  89.5% vs. 76.5%

✓ Spain, Italy: Hybrid vs. Concomitant
  ITT: 90%, PP: 92% vs. ITT: 91.7%, PP: 96%

Quadraple treatment with Bismuth

PPI X2 + Bi X4 + TET X4 + MET X3
for 10-14 days

Eradication rate in Greece: 78%
Quadruple treatment with Bismuth
Disadvantages

✓ Tetracyclin and Bismuth salts not available

✓ Doses and duration not adequately defined

✓ Side effects

✓ Bad compliance

Quadruple regimen with a capsule contained Bi-TET-MET

- Multicenter trial with 440 patients
- OME X2 + capsule X4 vs. classic triple

80% ↓ 55%

Treatment regimens with Quinolones

✓ Mostly Levofloxacin

✓ In triple, sequential, concomitant and quadruple regimens

✓ Duration: 5-14 days

✓ Success rate: 78-93%

✓ Disadvantages: Increasing resistance, side effects, cost

Graham DY, et al. CGH 2014; 177
Levofloxacin as a second-line treatment
(eradication rate: 74 – 86%)

✓ Spain: 74% (ITT) in 1000 pts.  
  Gisbert, J Clin Gastroenterol 2013
✓ Taiwan: 78%  
  Chuah, Helicobacter 2012
✓ Taiwan: 14 days 86%  
  Chuah, Helicobacter 2012

✓ Meta-analysis in 2,500 patients:
  
  LEVO 76.5%  Quadruple with Bi: 67%  
  Di Caro, World J Gastroenterol 2012
Treatment regimen should be selected according to areas of low and high clarithromycin resistance (Clari\textsuperscript{R}).

Regions with low Clari\textsuperscript{R} prevalence:

1\textsuperscript{st} line
- PPI-Clari-Amoxicillin/Metronidazole or Bismuth Quadruple

2\textsuperscript{nd} line
- Bismuth Quadruple
  - or
  - PPI-Levofloxacin/Amoxicillin

3\textsuperscript{rd} line
- Based on susceptibility testing only

Regions with high Clari\textsuperscript{R} prevalence:

1\textsuperscript{st} line
- Bismuth Quadruple
  - if not available:
    - non-Bismuth Quadruple (either sequential or concomitant)

2\textsuperscript{nd} line
- PPI-Levofloxacin/Amoxicillin

3\textsuperscript{rd} line
- Based on susceptibility testing only
Reinfection

- Reinfection following successful bacterial cure is unusual

- Commonly represents recrudescence of the original bacterial strain

- In adults, reacquisition of the bacteria occurs in <2%/persons/year which is similar to the rate of primary infection in adults
Future?

- Targetted novel therapies – role of functional genomics

- *H. pylori* virulence factors – use in clinical practice

- Vaccination – prophylactic & therapeutic vaccination (animal models)
Key points (1)

-> *H. pylori* is a flagellated spiral micro-aerobe
-> Infection is a risk factor for gastric cancer
-> Causes PUD and gastritis
-> Produces a cell-damaging toxin
-> Transmission route is unclear
-> Dz rates are falling in industrialised countries
-> Tx is by eradication using combination therapy
Key points (2)

- There is still no ideal empirical treatment.

- Increasing antibiotic resistance is a serious unresolved problem even with the new therapeutic regimens.

- Extending the duration of treatment to 14 days seems to increase efficacy.

- Concomitant quadruple treatment without bismuth seems to represent the currently best therapeutic option in Greece.