Helicobacter pylori: From its discovery to a revolution in gastroenterology

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Peptic ulcer and Nobel prize…over more than a century

- The presence of HCl in the stomach by W. Prout in 1823
- Vagus plays crucial role in gastric HCl secretion by T.P. Parker in 1895
- Gastrin is gastric HCl stimulant by J.S. Edkins in 1905
- Do In; NO ACID NO ULCER by K. Schwartz in 1910
- Histamine as gastric HCl secretagogue by L. Popielki in 1916
- H₂-receptor antagonists by J.W. Black in 1972 and proton pump inhibitors by G. Speirs in 1980 showing strong inhibition of HCl secretion stimulated by various secretagogues and anti-ulcer efficacy

Fig. 1. Historical background; major discoveries in gastroenterology (star indicates Nobel prize)
**H. pylori: Some key dates**

<table>
<thead>
<tr>
<th>Microscopic observation of spiral-shaped bacteria in stomach</th>
</tr>
</thead>
<tbody>
<tr>
<td>1893 Bizzozero animal</td>
</tr>
</tbody>
</table>

**Culture**

| 1982 Marshall human |

**Nomenclature**

| 1982 Marshall *Campylobacter pyloridis* | 1989 Goodwin *Helicobacter pylori* |
Evolution of Number of publications on *H. pylori* and gastroduodenal diseases

N = > 22,000 articles listed in PubMed

The milestone publications...

Organisms present in gastric biopsies from:
- 100% of duodenal ulcers
- 80% of gastric ulcers
- 90% of active chronic gastritis
- 3% with no histological gastritis

*H. Pylori* on gastric epithelial cells

**The Lancet** • Saturday 16 June 1984

**UNIDENTIFIED CURVED BACILLI IN THE STOMACH OF PATIENTS WITH GASTRITIS AND PEPTIC ULCERATION**

**HARRY J. MARSHALL**

J. ROBIN WARREN

Departments of Gastroenterology and Pathology, Royal Perth Hospital, Perth, Western Australia

Summary Biopsy specimens were taken from intact areas of antral mucosa in 97 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 peptic ulcers, peptic ulcer disease, and other gastrointestinal diseases.

Fruitless attempts to culture the elusive organism until …

Culture of gastric mucosa biopsies from 34 patients negative (after 48 h)

[Image: Royal Perth Hospital]

First cultures became positive only after prolonged Easter week-end

Resistance from the medical establishment…

…but was accepted to the 2nd International Microbiology Workshop on *Campylobacter* infections in Brussels in 1983

Submission to the 1983 meeting of the Australian Gastroenterological Society was rejected….
Attempts to fulfil Koch’s postulates (I)

Self ingestion of a pure culture of H. pylori (10⁹ organisms)

- Day 5: halitosis, nausea, vomiting of acid free gastric juice
- Day 10: Endoscopy with biopsy
  Acute gastritis with many H. pylori
- Day 14: Rx with Bismuth/tinidazole resolution of symptoms

Marshall BJ; Lancet 1988; 332; 1437-42

Attempts to fulfil Koch’s postulates (II)

Cimetidine vs Bismuth (CBS) (8 Wks) + Placebo or tinidazole (10d)

Eradication of H. pylori:
- increases healing of duodenal ulcer 92% (Hp-) vs 61% (Hp+)
- decreases relapse rates at 12 months 21% (Hp-) vs 84% (Hp+)

Marshall BJ; Lancet 1988; 332; 1437-42
Hill causality criteria for association between *H. pylori* infection and gastroduodenal ulcer

- Strong association
- Temporal relationship
- Major effects of therapeutic intervention on outcome
- Biologic plausibility
  - Biologic gradient?
  - But, no specificity of association

### H. pylori: Epidemiology

- Chronic infection
- Prevalence increases with age
  - incidence = 0.5-1% by person / year
- Infection acquired earlier in life and increased prevalence:
  - developing countries
  - populations with low socio-economic status
- Inter-human transmission
  - oral-oral and/or faecal-oral
Prevalence of *H. pylori* infection with age

![Bar chart showing prevalence of *H. pylori* infection with age.](chart.png)

Adapted with permission from Heatley, Helicobacter pylori and Gastrointestinal Disease; Oxford, UK: Blackwell Scientific Publications

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Divergent response to *H. pylori* infection

![Diagram illustrating divergent response to *H. pylori* infection.](diagram.png)

Chronic *H. pylori* Infection

- Antral predominant Gastritis: Acid & Gastrin, little or no atrophy, low risk of gastric Ca
- Corpus predominant Gastritis: MAG, Acid, Gastrin; high risk of gastric carcinoma

Mild Mixed Gastritis

- Normal Acid
- Duodenal ulcer disease
- No significant disease

?- Bacterial? Environment? Host
Major pathogenic factors of *H. pylori*

<table>
<thead>
<tr>
<th>Virulence factors</th>
<th>Function</th>
<th>Present in all strains</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urease</td>
<td>Acid resistance; Nitrogen metabolism; Escape to immunologic response; Cytotoxic effect</td>
<td>Y</td>
</tr>
<tr>
<td>Flagella</td>
<td>Motility</td>
<td>Y</td>
</tr>
<tr>
<td>BabA</td>
<td>Adhesion to Lewis b antigens</td>
<td>N</td>
</tr>
<tr>
<td>AlpA, AlpB</td>
<td>Adhesins (receptors not identified)</td>
<td>Y</td>
</tr>
<tr>
<td>Catalase</td>
<td>Superoxide dismutase; detoxification (escape to immunologic response)</td>
<td>Y</td>
</tr>
<tr>
<td>LewisX,Y antigens</td>
<td>Molecular mimicry (escape to immunologic response), adherence</td>
<td>N</td>
</tr>
<tr>
<td>VacA</td>
<td>Cytotoxicity</td>
<td>N</td>
</tr>
<tr>
<td>CagA</td>
<td>Immunodominant antigen, unknown function</td>
<td>N</td>
</tr>
<tr>
<td>Cag pathogenicity island</td>
<td>Secretion system (type IV); Induction of inflammation</td>
<td>?</td>
</tr>
</tbody>
</table>

Cag pathogenicity island

Censini et al., PNAS 1996, 93: 14648-53
Role of cag pathogenicity island and CagA protein

H. pylori

- Type IV secretion system
- CagA
- Polymerisation of actin filaments
- Induction of IL-8 secretion
- Arrangements of cytoskeleton
- Inflammation of gastric mucosa
- Cellular proteins
- Apoptosis
- Nucleus
- Gastric epithelial cell

(Covacci et Rappuoli, 2000)

H. pylori genome

(Tomb et al. 1997, Alm et al. 1998)

Assign function to a putative genes
**H.pylori**: from infection to gastric cancer

- **H.pylori**
  - Chronic active gastritis
  - Interaction DNA/mutagene
  - Atrophic gastritis
  - Intestinal Metaplasia
  - Dysplasia
  - Gastric Cancer

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**H. pylori** and gastric pathology

- **Pro-inflammatory cytokines**
  - Gene polymorphisms
    - IL-1β-511*T
    - IL-1RN*2/2
    - IL-10 ATA haplotype
    - TNF-α-308*A
    - IL-6-251*A

- **Innate immune response**
  - Gene polymorphisms
    - TLR4+3927*G

- **Bacteria promoted factors**
  - CagA, VacA
  - Endotoxins (LPS)
  - Growth factors, gastritox, COX-2-Prostaglandins
  - Reactive oxygen species

- **Environmental factors**
  - Smoking
  - Dietary factors
  - Abuse of stimulants

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*H. pylori* infection may be also responsible for gastric carcinogenesis that follows expression and action on gastric mucosa of cytotoxins (CagA and VacA), proinflammatory cytokines and gastritis.
June 1994

• Working group WHO/IARC

« Establishment of a definite link between H. pylori infection and gastric cancer in humans »

« H. pylori considered as Group 1 (definite) carcinogen »

IARC Monograph. - Evaluation of carcinogenic risks for humans - 1994, Lyon, France

H. pylori and gastric cancer

• Epidemiologic data
  – Geographic and temporal concordance in incidence

• Cross-sectional case-control studies
  – 50 -100 % of gastric cancers infected with Hp

• Prospective nested case-control studies
  – Hp infection --> Risk of developing gastric cancer increased 2- to 9-fold

• Causal relationship in animal model
  – mongol gerbils
The only good *Helicobacter* is a dead *Helicobacter*!

**Evolution of the understanding theories of gastroduodenal ulcers**

50-60’s

*No acid... No ulcer*  
(K. Schwartz 1910)

50-60’s

*No Helicobacter ...No ulcer*  
(B Marshall, 1988)
**H. pylori infection:**
Therapeutic indications

- Peptic ulcer disease* – active or not
- Gastric MALT lymphoma
- Atrophic gastritis
- Post-gastric cancer resection
- First degree relatives of gastric cancer patients
- Patient’s wishes – after full consultation with their physician

Hp eradication Rx cost-effective*:  > anti-H2 blockers for healing ulcers = to maintainance Rx for preventing recurrences) (1-2 yrs)

*Meta-analysis CRG, Ford, AJG 2004

**Characteristics of optimal drugs for the treatment of H. pylori infection**

- High in vitro antibacterial activity
- High concentration in gastric mucosa/mucus
- Active by endoluminal and systemic routes
- Stable over wide range of pH (<2-7)
- Good tolerance / few side effects
- Low propensity for resistance
- Inexpensive
### First choice antibiotics

<table>
<thead>
<tr>
<th>Clarithromycin</th>
<th>Amoxicillin</th>
<th>Metronidazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most active single agent</td>
<td>No resistance development</td>
<td>Activity not influenced by pH</td>
</tr>
<tr>
<td>Good diffusion in gastric mucosa</td>
<td>Activity not affected by acidic pH</td>
<td>Clinical efficacy little affected by resistance</td>
</tr>
<tr>
<td>Synergy with acid-suppressive agents</td>
<td></td>
<td>Inexpensive</td>
</tr>
<tr>
<td>Increasing resistance</td>
<td>Broad-spectrum</td>
<td>Side effects (gastrointestinal)</td>
</tr>
<tr>
<td>Decreased efficacy in areas of high resistance (20%)</td>
<td>Side effects (gastrointestinal, dermatologic)</td>
<td>High resistance rates in several areas (&gt;40%)</td>
</tr>
<tr>
<td>High cost</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Second choice antibiotics

<table>
<thead>
<tr>
<th>Tetracyclines</th>
<th>Fluoroquinolones</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resistance rare</td>
<td>Potential interest for rescue therapy if previous treatment failures</td>
</tr>
<tr>
<td>Synergy with bismuth salts</td>
<td>Well tolerated</td>
</tr>
<tr>
<td>Clinical efficacy in quadruple therapy</td>
<td></td>
</tr>
<tr>
<td>Inexpensive</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Side effects (gastrointestinal, rash)</td>
<td>Wide usage of FQ in other indications</td>
</tr>
<tr>
<td></td>
<td>Poorly active at acidic pH</td>
</tr>
<tr>
<td></td>
<td>Resistance increasing</td>
</tr>
</tbody>
</table>
Proton-pump inhibitors

- Bacteriostatic activity against *H. pylori*
- Synergy with some antimicrobials (metro, clari, tetra)
- Effect of acid suppression (↑ gastric pH):
  - Increases activity of several antibiotics (macrolides, quinolones)
  - Improved penetration of bismuth salts in gastric mucosa
  - Increased concentrations of metro, clari, tetra in the stomach
- Improve clinical efficacy of dual antimicrobial regimens

Adjuvant effect of Omeprazole on *H. pylori* eradication by amoxicillin

Unge, Bordeaux 1988
Therapeutic principles (1)

Rational choice of therapeutic agents

- Based on clinical experience
- Association regimens including:
  - amoxicillin
  - clarithromycin
  - 5-Nitroimidazoles
  - Tetracycline
  - Bismuth salts
- Other agents active in vitro have proven ineffective in vivo

Hp : Therapeutic Principles (2)

Importance of drug associations

<table>
<thead>
<tr>
<th>Drug Association</th>
<th>% Eradication (ITT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mono (2-4 wks)</td>
<td>15</td>
</tr>
<tr>
<td>Bi (2 wks)</td>
<td>60</td>
</tr>
<tr>
<td>Tri (1 wk)</td>
<td>85</td>
</tr>
<tr>
<td>Quadri (1 wk)</td>
<td>88</td>
</tr>
</tbody>
</table>
Hp : Therapeutic principles (3)

Treatment duration: eradication rates with bismuth based triple therapies

% eradication (PP)

MTZ resistant
MTZ susceptible

Days

Hp : Therapeutic principles (4)

Importance of resistance on Hp eradication

% eradication (PP)

Mégraud, Gut 2004
Importance of patients compliance for eradication of *H. pylori*

![Graph showing eradication rates for different compliance levels and ulcer types.](image)

Factors of importance for predicting outcome of therapy in Hp infection

<table>
<thead>
<tr>
<th>PROVEN</th>
<th>POSSIBLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Choice of agents</td>
<td>Drug formulation</td>
</tr>
<tr>
<td>Choice of associations</td>
<td>Number of daily administration</td>
</tr>
<tr>
<td>Compliance</td>
<td>Drug intake in relation to meal</td>
</tr>
<tr>
<td>Antimicrobial resistance</td>
<td>Polymorphism of CYP2C19 in metabolism of PPIs</td>
</tr>
<tr>
<td>Dosage</td>
<td></td>
</tr>
<tr>
<td>Duration of therapy</td>
<td></td>
</tr>
</tbody>
</table>
First line therapy

1 week, Triple therapy, 2x/daily
(PPI + 2 ABs)

PPI standard dose bid (omeprazole, lanso, panto)
+ Clarithromycin 500 mg bid (C)
Amoxicillin 1000 mg bid (A)
+ or
Metronidazole 500 mg bid (M)

CA preferred in area with Metro-R > 40%

≥ 80% cure rates on ITT to basis

Maastricht 2005-3 consensus report
Malfertheiner, APT 2002

Primary resistance rates of H. pylori in Belgium

(N=151, 10 centres)

Belgian Helicobacter Study Group, 2004
Antimicrobial resistance of \textit{H. pylori} in Europe

Glupczynski, EJCMID 2001

Risk factors for resistance

\textbf{Metro-R}
- Born outside Europe (OR: 2.7)
- Living in East. Europe (OR: 1.9)
- Female (OR: 2.3)

\textbf{Clari-R}
- Living in South. Europe (OR: 2.3)
- Age < 12 yrs (OR: 1.8)

22 centres, 17 pays
N=1274 (N° d’isolats/Centre = 64, valeurs extrêmes: 21-115)

Consumption of macrolides in 17 European countries in 1998

www.ua.ac.be/ESAC
Secondary resistance of *H. pylori* after eradication failure

<table>
<thead>
<tr>
<th>% resistance (N=225)</th>
<th>Amox</th>
<th>Clari</th>
<th>Métro</th>
<th>Clari + Métro</th>
</tr>
</thead>
<tbody>
<tr>
<td>first Rx: PPI-AC (90% cases)</td>
<td>64</td>
<td>53</td>
<td>37</td>
<td></td>
</tr>
</tbody>
</table>

Mégraud et al. Gut 2001

Second line therapy

Bismuth quadruple therapy, 10-14 d

- Failure, allergy, intolerance, high level of resistance to clari

- PPI standard dose bid (omeprazole, lanso, panto)
- Bismuth salt (CBS) 120 mg qid
- Metronidazole 500 mg tid
- Tetracycline 500 mg qid
- or
- Amoxicillin 500 mg tid

Unaffected by Clari-R; little influenced by Metro-R

Cost < to PPI-triple therapy

≥ 85% cure rates on ITT to basis

Fishbach, APT 2004
Rescue therapy

after failure of two courses of different therapies

Treatment adjusted on the basis of culture and susceptibility results (antibiogramme)

Should be handled on « Case-by-case » basis

Avoid re-using same agents (clari, metro)

Proposed triple therapies (under evaluation):
PPI + Amox + fluoroquinolones (Levoflo, Moxiflo)
rifamycins (rifaximin, rifabutin)

Evolution of *H. pylori* resistance

Bontems et al., PIJD 2001
Evolution of prevalence of *H. pylori* infection in Europe

<table>
<thead>
<tr>
<th>Year of birth</th>
<th>% <em>H. pylori</em> +</th>
</tr>
</thead>
<tbody>
<tr>
<td>1925</td>
<td>40</td>
</tr>
<tr>
<td>1935</td>
<td>40</td>
</tr>
<tr>
<td>1945</td>
<td>38</td>
</tr>
<tr>
<td>1955</td>
<td>33</td>
</tr>
<tr>
<td>1965</td>
<td>28</td>
</tr>
<tr>
<td>1975</td>
<td>22</td>
</tr>
</tbody>
</table>

Perspectives

- *H. pylori* infection becoming more rare
- Consequences of infection in terms of burden of associated diseases (ulcer, cancer) is going to be with us for a while
The *H. pylori* saga ending in a Nobel Prize ….

- …Being at the right place at the right time, and seeing what other people had seen but thinking what nobody else thought…

- The role of chance…

- … »Challenging established dogmas with passion, tenacity and prepared mind …

- Possibility of making important discoveries as clinicians in the course of daily practice…