Helicobacter pylori (Hp)

- Gram negative spiral flagellate
- Infection of gastric epithelium
  - Stomach mucosa exclusively
  - Duodenal gastric metaplasia
  - Esophageal gastric metaplasia
- Helicobacter pylori cause of chronic gastritis
- Usually asymptomatic
Helicobacter pylori penetrates the gastric mucus layer

Arrow: Helicobacter pylori between mucus layer and mucosal cells
Helicobacter pylori attach only to gastric epithelial cells
Helicobacter pylori virulence factors
Immunoblot of patient with duodenal ulcer
Usually CagA and VacA present
Host response not yet specified
Mechanism of disease

- Helicobacter pylori persists for life in the stomach after initial acute infection unless treated
- Strict host and tissue trophism
- Urease positive Hp only can colonize the stomach
- Flagella is necessary for movement and colonization
- Cag A (Cytotoxin-associated gene A) related to virulence (60% strains positive in developed countries, 90% in developing countries)
  - Straight correlation to peptic ulcer likely, cancer not established
- Vac A (Vacuolating cytotoxin)
  - Straight correlation to peptic ulcer likely, cancer not established
Natural history of a Helicobacter infection

Symptoms
Initial Acute Helicobacter pylori infection

• Vague epigastric discomfort
• Vomiting
• Symptoms settle after several days
• Usually passes unnoticed or asymptomatic
Initial asymptomatic gastritis
Acid output not different from healthy subjects, except
Duodenal ulcer patients have higher acid output
Gastric cancer patients lower acid output than healthy subjects
Active chronic Helicobacter pylori gastritis

- Achlorhydria in beginning reversible
- No clearance of Helicobacter pylori leads to chronic (re)infection
- With neutrophil infiltration and damage of glands
- Antrum more susceptible to severe gastritis
- Gastric mucosal cells replaced by intestinal cells and fibrosis
- Chronic atrophic gastritis developed countries at old age
Active chronic Helicobacter pylori gastritis

• Children in developing countries
• Early age Hp acquirement enhances chance for developing atrophic gastritis and achlorhydria at young adult age in developing countries

• Symptoms:
  – Growth impairment
  – Iron deficiency
  – Susceptibility to enteric infections
Achlorhydria and Hp

- Iron deficiency anemia due to achlorhydria
- Iron not reduced to ferrous state to facilitate absorption
- Treatment of Hp improved iron deficiency anemia
- Late complications are Vitamin B12 deficiency due to achlorhydria Vit B12 not removed by acid from food in stomach
Iron deficiency

• Treatment of Hp recovers iron deficiency
• Iron treatment in Hp does not improve without Hp treatment
• Some controversy persists
Prevalence of Helicobacter infection

• Ethiopia 1000 children followed from birth to age 5 years
• Prevalence of Hp at 3 years 17%
• Inverse relationship to allergies
• Sweden children 2%
Nigeria Lagos hospital cohort

• Children seropositive for H. pylori 63.6%

• Prevalence of H. pylori infection increased significantly from 40.4% in children less than five years of age to 85.1% at six to ten years of age

• H. pylori infection was associated with low social class (OR = 3.24) and with RAP (OR = 3.47)

• No association was observed with exclusive breastfeeding, duration of breastfeeding, and under-nutrition
In developed countries prevalence decreasing
Most patients are above 50 years
New cases immigrants from high risk countries
Helicobacter pylori transmission

- **Oral-oral transmission unlikely**
- Dentists negative
- Doctors positive
- No transmission between couples
- No higher transmission among teenagers

- **Gastric-oral transmission** through vomiting possible but unlikely important cause

- **Fecal-oral transmission** most important route
- Water Peru, Mexico, Japan, Sweden Hp positive
Person to person transmission

- Genotyping infection transmission:
  - Developed countries mother to child
  - Developing countries other route probably fecal-oral route
- Child to child, mother to child, father to child
- All possible and described
Epidemiology/Prevalence

• Infected persons:
  – Developing countries > 70%
  – Developed countries < 30%

• Acquired in childhood by fecal-oral route (rarely mouth, vomitus, aerosol (PCR Hp in feces children The Gambia and water in Peru))

• Infection rate 15% per annum in developing countries

• Rate of reinfection after treatment:
  – Developed countries low, but might be 5%
  – Developing countries 30% within 30 month period due to new infections (different DNA Hp)
Helicobacter pylori associated diseases
Helicobacter pylori positive
Symptoms duodenal ulcer disease
Gastritis causes almost no symptoms

• Endoscopic proven duodenal ulcer disease in children

• 90%
  – Episodic epigastric pain
  – (Recurrent) Vomiting
  – Nocturnal awakening
  – Hematemesis (NSAID’s?)

• 55%
  – Abdominal pain only
Correlation to chronic abdominal pain

- No correlation found in children with chronic abdominal pain and Hp infection
- Treatment of Hp infection did not influence chronic abdominal pain over one year measured
- In Helicobacter pylori gastritis suggestion of ulcer pain, severe, epigastric, during night symptoms might be related to Hp infection
Helicobacter pylori infection

• Hp causes inflammation with intraepithelial neutrophils damaging mucosal cells
• Hp causes only inflammation of gastric epithelial cells
• Gastric atrophy means epithelial cells of gastric glands are replaced by fibrosis
• Intestinal metaplasia is separate from atrophy
• Duodenal ulcers are in gastric metaplasia in duodenum
• Duodenal ulcers, Hp 90% present in antrum stomach
• Gastric ulcers due to Hp rare in children
Peptic ulcer correlations

• Duodenal ulcers only occur in duodenal gastric metaplastic mucosal cells
• Duodenal ulcers only occur in Helicobacter pylori antrum gastritis
• Treatment of helicobacter antrum gastritis cures duodenal ulcers
• No proof exists of correlation of gastric ulcer and Helicobacter pylori gastritis (only adults related to other causes)
Peptic Ulcers in Helicobacter pylori in children

- **Primary duodenal ulcer disease**
- < 10 years old rare
- 10-18 years some
- Related to Helicobacter pylori

- **Primary gastric ulcer disease in children**
- Rare
- Not related to Helicobacter pylori
Peptic ulcer

Primary Peptic Ulcer Disease

*H pylori*

Secondary Peptic Ulcer Disease

Eosinophilic

Granulomatous

NSAID’s

Aspirin

Henoch Schoenlein Purpura

Collagenous gastritis

Cytomegalovirus gastritis

Ulcer Disease Due to Hypersecretory State

Zollinger Ellison
Gastritis in children
Infectious causes

- Cytomegalovirus hypertrophic gastropathy with proteinloosing and oedema due to low albumin with spontaneous recovery
- Treponema pallidum
- Histoplasmosis
- Influenza A might cause bleeding gastric ulcerations with haematemesis
- Tuberculosis
Prevalence of Peptic Ulcers in Helicobacter pylori infection

- Prevalence in Europe in Hp infected children
  - < 6 years: 3.5%
  - 6-11: 4.6%
  - >11 years: 10.4%
- Turkish children: 27%
- NSAID’s in Hp treated negative children
- Africa: unknown
Gastric cancer

• Increased risk
  – More predominant corpus gastritis
  – Reduced gastric acid production
  – Gastric mucosal atrophy

• Reduced risk
  – Antral predominant gastritis
  – Normal or high gastric acid production
Cancer risk

• In Africa no increased prevalence of gastric cancer
• High Helicobacter pylori prevalence
• CagA toxin positive strains are associated with duodenal ulcer (high acid state)
• CagA toxin positive strains are associated with gastric cancer (low acid state)
• Duodenal ulcer protects for cancer development
• Correlation to hypochlooorhydria, strains, genetics of host, nutritional status
Helicobacter pylori genetics and Gastric Cancer

• Western type=African type
• CagA are expected to be hpEurope, hpNEAfrica, hpAfrica1 or hpAfrica2 type strains
• Vac-m1a type is typical in Europe and Africa

• Is about toxicity of strains
• If less toxic means less mucosal atrophy
• And less gastric cancer
Prevalence of atrophic gastritis in children in Africa
Probably low <5%?
Endoscopies in adults and children

- Mulago hospital Uganda all ages
  - Hp gastritis 25%
  - Atrophic gastritis 5%
- Ouagadougou Burkina Fasso Endoscopy in children
  - Mild atrophic gastritis 38%
  - Duodenal ulcers 3%
- Awolowo University Nigeria all ages
  - Gastric atrophy 5%
  - Intestinal metaplasia 10%
Gastric Cancer

• Families with gastric cancer or MALT lymphoma should not be screened for Hp
• Gastric atrophy is related to gastric cancer development
  – Treatment of Hp before atrophy has developed
• Familial forms of gastric cancer
  – IL-1β mutations are related to gastric cancer (IL-1β is strong acid inhibitor)
  – E-Cadherin gene mutations are related to familial gastric cancer
Mucosal Associated Lymphoid Tissue
MALT lymphoma

- Gastric lymphoma related to Hp infection
- MALT lymphoma complete resolution in 75% of patients by Hp treatment
- (11;18)(q21;q21) translocation does not respond and needs chemotherapy
- Other rare lymphomas:
  - B-cell lymphoma, EBV, immune suppression, HIV
  - T-cell lymphoma in antrum with large ulcer
Cancer reduction by helminths

- Helminths reduce gastric metaplasia
- Heligmosomoides polygyrus inhibits progression of inflammation into premalignant lesions
- Microbiota increase premalignant lesions
Gastric MALT Lymphoma
Usually located in the antrum
(T-cell lymphoma also with large ulcers in antrum)
Detection tests available

Detection of Helicobacter Pylori

- Gastroscopy biopsy
- Giemsa
- Wurthin-Starry stain
- Urease
- Culture
- Breath tests
- Antibody response

Stool Antigen Test
Helicobacter pylori
Endoscopic and Biopsy picture

Giemsa
Wurthin-Starry
Scanning EM
Hp Breath test, $^{14}\text{C}$ low radiation risk
$^{13}\text{C}$ mass spectrometer needed
## Confidence limits of available Hp tests

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<tr>
<th>Tests</th>
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<th>Positive Predictive Value (%)</th>
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Testing
Practical points

• Endoscopy/biopsy  Sampling error, antibiotic sensitivity
• Urea breath test  Cooperation needed
• Stool Hp antigen  Clarythromycin sensitivtity
• Hp antibodies  Antibodies may persist after infection for some time in very young children

• None 100% sensitive and specific
Treatment indication

• Peptic ulcer disease
• Cancer risk
• Chronic disease risk
• Non-ulcer dyspepsia
• Atrophic gastritis
• Gastric MALT lymphoma
• Unexplained iron deficiency anemia and ITP
• Patients on long term NSAIDS who have GIT bleeding and/or peptic ulcer
Eradication recommendations

*Disease:*
- Peptic ulcer disease
- Atrophic gastritis reversible
- Gastric lymphoma

*Treatment indication:*
- Sanitation improvement
- Prevention of ulcer recurrence for 1-2 years
- Intestinal metaplasia cannot be reversed
- (Atypical) dysplasia as early stage of gastric atrophy can be reversed, also in presence of intestinal metaplasia
- Lymphoma only regresses when Hp is eradicated
Drugs effective for *Helicobacter pylori*

<table>
<thead>
<tr>
<th>Group</th>
<th>Description</th>
<th>Duration</th>
</tr>
</thead>
</table>
| A<sup>a</sup> | Bismuth  
• Bismuth subsalicylate (Pepto Bismol) 525 mg (2 tablets) qid  
• Bismuth subcitrate (DeNol) 120 mg (1 tablet) qid | 14 days |
| B     | Penicillin  
• Amoxicillin IG bid | 7 or 10 or 14 days |
| C     | Macrolide  
• Clarithromycin 500 mg bid<sup>c</sup>  
• Josamycin 1000 mg bid | 7 days |
| D     | Nitroimidazole  
• Metronidazole 500 mg  
• Tinidazole 1000 mg daily | 7 or 10 or 14 days |
| E     | Tetracycline  
• Tetracycline 500 mg qid | 14 days |
| F     | Quinolone  
• Ofloxacin 500 mg bid  
• Levofloxacin 250 mg bid | 7–14 days |
| G     | Nitrofurans  
• Furazolidone 200 mg bid<sup>c</sup> | 7 or 10 or 14 days |
| H     | Ansamycin  
• Rifabutin 150 mg bid | 14 days |
| I     | Proton pump inhibitors (use double a normal dose)  
• Omeprazole 40 mg tid (has been superseded by esomeprazole in most countries)  
• Esomeprazole 40 mg tid  
• Lansoprazole 30 mg tid  
• Pantoprazole 40 mg tid  
• Rabeprazole 20 mg tid | 14 days |

*<sup>a</sup>Treatment priorities are normally HPG (HPG or IPD) or IPGC. Esomeprazole is used in the US and other countries.*
Common regimes used for eradication of Helicobacter pylori

<table>
<thead>
<tr>
<th>Common Regime 1</th>
<th>Common Regime 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esomeprazole 20 mg bid, clarithromycin 500 mg bid, and amoxicillin 1 g bid (7–10 days)</td>
<td>Rabeprazole 20 mg bid, amoxicillin 1 g bid, levofloxacin 250 mg bid (10 days)</td>
</tr>
<tr>
<td>Esomeprazole 20 mg bid, clarithromycin 250 mg bid, and metronidazole 400 mg bid (7 days)</td>
<td>Omeprazole 20 mg bid, amoxicillin 1 g bid, furazolidone 200 mg bid, and bismuth subsalicylate (De-Nol) 240 mg (2 tabs) bid (14 days)</td>
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<td>Bismuth (subsalicylate or citrate) 1 tablet qid,(^a) tetracycline 500 mg qid, metronidazole 250 mg qid (1–1.5 g daily) (10–14 days)</td>
<td>(^a)Addition of a proton pump inhibitor probably enhances the cure rate. bid, twice a day; qid, four times a day.</td>
</tr>
</tbody>
</table>

---

\(^a\)Addition of a proton pump inhibitor probably enhances the cure rate. bid, twice a day; qid, four times a day.
Eradication of Hp

- European children 66%
- With peptic ulcer disease 80%
- Sensitivity tested for Clarithromycin/Metronidazole 93%
- Antibiotic resistance test
- Regimes:
  - Amoxicillin/Clarithromycin/PPI
  - Amoxicillin/Imidazole/PPI
  - Bismuth/Amoxicillin/Imidazole
- Sequential therapy 97%
  - PPI+Amoxicillin 5 days followed by
  - PPI+Clarithromycin+Tinidazole 5 days
Doses mg per kg/day

- **Amoxicillin** 50
- **Clarithromycin** 20
- **Metronidazole** 20
- **PPI** 1-2
- **Bismuth Subcitrate** 8
  - 480 mg/1.73 m² or 120 mg BID, above 10 years
  - 240 mg BID, Bismuth levels within normal range
  - no adverse event ever reported in children
Eradication recommendations

- Peptic ulcer disease
- Atrophic gastritis reversible
- Gastric lymphoma

- Therapeutic recommendations:
  - Duration 7-14 days
  - Proton Pump Inhibitors: Acid protects Hp
  - Antibiotics with no resistance: Combination of two antibiotics
    - Amoxicillin
    - Bismuth
    - Furazolidone
    - Tetracycline
  - Antibiotics with rapid resistance:
    - Metronidazole, Clarithromycin, Rifabutin
Follow up

• Repeat test after 8-12 weeks

• Still positive for Hp:
  – Non compliant
  – Resistance

• Consider different regime or add more antibiotics, quadruple regimes

• Longer treatment 14 instead of 7 days
Vaccination

- At early infancy
- No natural elimination of Hp known
- CagA and VacA with enhancement factors possible vaccine
- No clue for solution yet
Thank you
Eradication of Helicobacter Pylori and Healing of Duodenal Ulcer

- H. pylori Eradication
- Ulcer Healed

% of Patients

- Cimetidine
- Cimetidine + Tinadazole
- Bismuth
- Bismuth + Tinadazole

10 wks
10 wks
12 mos
### Table 23.1 Accuracy of Diagnostic Tests for *Helicobacter pylori* Infection in 268 Patients Undergoing Esophagogastroduodenoscopy

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\(^a\)Chronic inflammation present in gastric antral biopsies.
\(^b\)Acute inflammation present in gastric antral biopsies.
\(^c\)Warthin–Starry stain of gastric antral biopsy.
\(^d\)Rapid urease test conducted on gastric antral biopsy with results ascertained at 24 hours.
\(^e\)\(^{13}\)C-urea breath test 60 minutes after administration of 150 mg \(^{13}\)C-labeled urea.
\(^g\)Serum antibodies to *H. pylori*
Detection of Helicobacter Pylori

Giemsa or Wurthin-Starry stain

Urease

Culture

Breath tests

Antibody response
Helicobacter Pylori
Helicobacter Pylori Gastritis

Supportive Evidence
- Biopsy
- Bacteriology
- Self-infection
- Serology
- Electron microscopy
- Response to antibiotics
<table>
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*Addition of a proton pump inhibitor probably enhances the cure rate.*

*bid, twice a day; qid, four times a day.*
In older persons infection reflects childhood acquisition similar to developing country incidence.
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<tr>
<td>Biopsy: chronic inflammation(^a)</td>
<td>100</td>
<td>66.3</td>
<td>84.4</td>
<td>100</td>
</tr>
<tr>
<td>Biopsy: acute inflammation(^b)</td>
<td>86.7</td>
<td>93.7</td>
<td>96.2</td>
<td>79.5</td>
</tr>
<tr>
<td>Biopsy: Warthin–Starry silver stain(^c)</td>
<td>93.1</td>
<td>99.0</td>
<td>99.4</td>
<td>88.7</td>
</tr>
<tr>
<td>CLOtest(^d)</td>
<td>89.6</td>
<td>100</td>
<td>100</td>
<td>84.1</td>
</tr>
<tr>
<td>Noninvasive</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(^{13})C-urea breath test(^e)</td>
<td>90.2</td>
<td>95.8</td>
<td>97.5</td>
<td>84.3</td>
</tr>
<tr>
<td>Fecal antigen test(^f)</td>
<td>94.1</td>
<td>93.4</td>
<td>93.4</td>
<td>92.6</td>
</tr>
<tr>
<td>Serum IgG(^g)</td>
<td>91.3</td>
<td>91.6</td>
<td>95.2</td>
<td>85.3</td>
</tr>
<tr>
<td>Serum IgA</td>
<td>71.1</td>
<td>85.3</td>
<td>89.8</td>
<td>61.8</td>
</tr>
</tbody>
</table>

\(^a\)Chronic inflammation present in gastric antral biopsies.

\(^b\)Acute inflammation present in gastric antral biopsies.

\(^c\)Warthin–Starry stain of gastric antral biopsy.

\(^d\)Rapid urease test conducted on gastric antral biopsy with results ascertained at 24 hours.

\(^e\)\(^{13}\)C-urea breath test 60 minutes after administration of 150 mg \(^{13}\)C-labeled urea.


\(^g\)Serum antibodies to H. pylori.

Eradication of Helicobacter Pylori and Healing of Duodenal Ulcer

H. pylori Eradication

Ulcer Healed

% of Patients

100
80
60
40
20
10 wks
10 wks
12 mos

Cimetidine
Cimetidine + Tinadazole
Bismuth
Bismuth + Tinadazole
Helicobacter Pylori Gastritis

Supportive Evidence

- Biopsy
- Bacteriology
- Self-infection
- Serology
- Electron microscopy
- Response to antibiotics
Achlooorhydria and Hp

- Iron not transformed in ferrous state
- Vitamin B12 not removed from food by lack of gastric acid
Peptic ulcer

- Helicobacter pylori
- NSAID’s
- Zollinger-Ellison