HELICOBACTER PYLORI UPDATE

PROF. TAWHEED MOWAFY
DEAN OF AZAL FACULTY OF MEDICINE
(H. pylori) is recognised as the most common chronic human bacterial infection, affecting up to 50% of the world’s population.

H. Pylori (initially called Campylobacter pyloridis) and its association with gastritis was first discovered in 1982. It has been said that its discovery represents one of the most important developments in medicine of the past century.
H. pylori plays a crucial role in the pathogenesis of upper GI disease including gastritis, peptic ulcer disease (PUD) and gastric cancer.

Eradication of H. pylori can lead to a reduction in the occurrence of PUD and prevention of gastric cancer.

In recent years there is increasing concern that the eradication treatment is failing and that there is increasing antimicrobial resistance.
H Pylori Overview

- History
- Structure
- Bacteriology
- Pathology of PUD
- Transmission
- Diagnosis
- Treatment

*Courtesy of the Helicobacter Foundation
1875: German scientists found helical-shaped bacteria living in the lining of the stomach but could not culture it.

1893: Italian scientist Giulio Bizzozero found helical shaped bacteria in acidic environment of dog’s stomach.

1899: Walery Jaworski of Jagiellonian University found helical shaped bacteria in human gastric washings: named it Vibrio Rugula.

- He was the first to suggest connection between bacteria and gastric diseases.
- Written up in “Handbook of Gastric Diseases” in Polish.

Isolated the bacteria from stomach and first to successfully culture it.

In their original paper (1983), concluded that ulcers and gastritis were from H Pylori and not stress and spicy food.
Medical community couldn’t believe a bacteria could survive the acidity.

Marshall drank a petri dish of H pylori, developed gastritis symptoms, recovered the bacteria from his stomach lining, and 10 days later had endoscopy where found signs of gastritis and H pylori.

He then treated himself with Bismuth and Metronidazole.
1994: NIH published their opinion that most gastric ulcers were from H pylori and that antibiotics should be used for treatment

2005: Marshall and Warren awarded Nobel Prize in Medicine

Of note, Marshall also worked at UVA for 10 yrs!
- Gram neg. helical-shaped bacterium 3 microns long with 4-6 flagella
- Microaerophilic (requires oxygen)
- Also coccoid forms found in culture
  - Thought to represent an adaptation to hostile surroundings
  - More resistant and enable to survive outside Human host (feces, drinking water)
BACTERIOLOGY: UREASE

- hydrolyzes gastric luminal urea to form ammonia that neutralizes gastric acid and forms protective cloud
- ammonium chloride and monochloramine also directly damages epithelial cells
- Also antigenic and activates human immune system which indirectly causes injury
- Urease: also basis for many diagnostic tests
BACTERIOLOGY

- Catalase: antioxidant and protects from toxic oxygen metabolites from activated neutrophils
- Protease: further degrade mucus
- Phospholipase: alter phospholipid content of gastric barrier to change surface tension, hydrophobicity, and permeability
- Receptor-mediated adhesion: Cag genes encode bacterial membrane proteins
Only 10-15% patients with H pylori infection will actually develop ulcer disease, indicating that bacterial strain is important.

Only strains with CagA can coexpress a vacuolating cytotoxin (VacA) toxin that can cause cell injury in vitro.

85-100% patients with DU have CagA+ strains, compared to 30-60% of infected patients who don’t develop ulcers.
- Another H pylori gene associated with developing DU
- Positive DupA have more intense antral inflammation, higher IL-8
- Also less gastric atrophy, intestinal metaplasia, and gastric ca (all associatedi with duodenal ulcer disease)
PATHOLOGY OF PUD

- Increased gastric secretion
- Gastric metaplasia
- Immune Response
- Mucosal defense mechanisms
Initially, hypochlorhydria but chronic infection leads to increased basal and stimulated acid output.

- Increased gastrin (trophic action on parietal cells and histamine-secreting enterochromaffin-like cells)
- Decreased somatostatin

However, hypergastrinemia alone not explain increased acid output: gastrin levels often return to normal within one month after eradication, while peak acid output still high.
Recall H Pylori is non-invasive but stimulates hearty inflammatory/immune response

Marked increase in platelet activation and aggregation: contribute to microvascular dysfunction and inflammatory cell recruitment

Antigenic substances: heat shock protein, urease, lipopolysaccharide (all activate T cells)

- Cellular disruption at epithelial tight junctions enhances antigenic presentation

Increased IL-1, IL-6, TNF-alpha, and most notably IL-8

- IL-8: chemotactic, activates, recruits neutrophils
IMMUNE RESPONSE

- Also stimulates B cell response (IgG and IgA) locally and systemically (role of local antibodies unclear)
- IgM antibodies: insensitive indicator of acute infection (and not clinically useful)
- IgA and IgG remain present while infection active and decrease after infection cured
- Antibodies to CagA protein detectable in gastric tissue and serum (more virulent organism)
H pylori downregulates epidermal growth factor (EGF) and transforming growth factor (TGF)-alpha: potent gastric acid inhibitors and stimuli of mucosal growth and protection

- After H pylori eradication, EGF sign. Increased: role in ulcer healing

Patients with DU have decreased mucosal bicarbonate production (not sure if from H pylori but once eradicated, bicarb output is normalized)

H pylori releases proteases that degrade protective mucous glycoproteins
Humans: major reservoir but seen in primates and domestic cats (may transfer to humans!)

Sheep: natural host?

- H pylori seen in milk and gastric tissue
- Higher infection rate in shepherds!
TRANSMISSION

- Person to person: isolations of genetically identical strains from multiple family members

- Fecal/oral: contaminated water in developing countries (H. pylori can remain viable in water for several days)

- Oral/oral: seen in dental plaque but prevalence is low
  - dentists don’t have higher prevalence

- Iatrogenic infection: from endoscopes
  - GI docs/nurses increased risk for H pylori infection!
PREVALENCE

- Conservative estimates: 50% of the world is affected
- Developing nations: majority of children infected before age 10 and prevalence of adults peaks at more than 80% after age 50
- In developed nations (US), infection in children unusual: increases to 10% between 18 and 30 years and 50% older than age 60
  - More common in blacks, hispanics
- Increased prevalence with older age thought to represent continuing rate of bacterial acquisition
  - But most evidence now states most infections are acquired in childhood even in developed nations
PREDISPOSING FACTORS FOR INFECTION

- Socioeconomic factors and living conditions early in life
  - Density of housing, overcrowding, number of siblings, sharing a bed, lack of running water

- Genetic factors
  - *H. pylori* patients who develop DU have higher parietal cell mass or sensitivity to gastrin than *H. pylori* positive healthy adults
  - May also determine duodenal cytokine response to infection
  - Monozygotic twins in different households greater concordance of infection than dizygotic twins

- Hereditary susceptibility: not proven

- Environmental factors: smoking, NSAIDS
Duodenal ulcers: h pylori detectable in at least 80-95% of patients with DU
  - Prevalence lower with complicated DU (ex. bleeding or perforation)

Gastric ulcers: 60-95%

Dyspepsia: 20-60%

Gastric Cancer: 70-90%

Asymptomatic patients: 20-45%
H PYLORI AND GERD

- Some suggest that H pylori positive patients have less GERD and esophagitis severity decreased
  - Also lower prevalence of Barretts metaplasia and esophageal adenocarcinoma
  - Further studies suggest that CagA strains are especially protective

- One mechanism purposed is that H pylori may modify gastric refluxate. Gastrin levels are higher and do not exhibit normal feedback inhibition
  - BUT Corpus-predominant gastritis reduces acid secretion (as opposed to antral-predominant); this is thought to be because of local inflammation
  - This eventually leads to hypochlorhydria and gastric atrophy
Potentially important observation is source of gastric cancer may not be from gastric epithelial cells themselves but from bone-marrow derived cells that differentiate into gastric epithelial cells in presence of H pylori.

Treating H pylori has been associated with reduction in cell proliferation, resolution of inflammation, disappearance of hyperplastic polyps, normalization of apoptotic rates, and regression of glandular atrophy intestinal metaplasia.
H PYLORI AND GASTRIC CANCER

- However, several studies show H pylori eradication may improve gastritis and superficial epithelial damage but degree of intestinal metaplasia and atrophy did not change (controlled trial in China).

- Another trial in China found that H pylori eradication did not decrease the overall incidence of gastric cancer during mean followup of 7.5 years.

Lyphoma: normal stomach does not have significant amount of lymphoid tissue but 
H pylori leads to aggregation of CD4+ lymphocytes and B cells

MALToma: especially seen in CagA+
- Remission of tumor with eradication of H pylori (but not all have complete remission possibly due 
to coexisting lymphoma)

Colon Ca: uncertain but maybe from high gastrin

Pancreatic Ca: especially with CagA+
Recommendations for diagnostic testing for H Pylori first purposed by National Institutes of Health (NIH) in 1994 with more recent guidelines in 1998 by ACG.

- H pylori is common in general population
- Diagnostic testing should only be performed if treatment is intended
- Testing only indicated with active PUD, past hx of documented PUD, or gastric MALT lymphoma
H Pylori present in majority of patients, especially if NSAIDS excluded

Thus, it is argued that no diagnostic method is cost-effective, and treatment should be empiric.

However, h pylori absent in up to 27% of patients with endoscopically proven duodenal ulcers
- Worse outcome especially when treated empirically

Thus confirmation of infection should be obtained
- Biopsy urease test
UNCOMPPLICATED GASTRIC ULCER

- H pylori neg. gastric ulcers increasingly recognized
  - Likely from unrecognized use of NSAIDS
- Test before antibiotic treatment
- Obtain biopsies from ulcer edge to exclude gastric cancer
  - Also at least 2 separate sites in gastric mucosa distant from ulcer to id H pylori
BLEEDING GU OR DU

- Should be tested for H pylori
- Although accuracy to detect may be affected with recent bleed
  - Sensitivity low but specificity high for biopsy-based methods like rapid urease test (67%, 93%), histology (70%, 90%), and culture (45%, 95%)
  - Noninvasive tests like urea breath test (93%, 92%), stool antigen test (87%, 70%), and serology (88%, 69%)
- Gastric mucosal biopsy suggested at initial endoscopy. If not obtained, start with urea breath test

If past hx documented by endoscopy or radiology but not treated for H pylori, test and then treat if positive

Reasonable to start with noninvasive test like breath test, serology, or stool
ASYMPTOMATIC PATIENTS AND FAMILY

- Usually not tested for H pylori
- Exception: family hx of gastric ca especially in Japanese, Chinese, Korean, and Russian descent (gastric ca incidence increased)
- Treating asymptomatic family members of patients with H pylori to reduce risk of reinfection: unclear
OTHER INDICATIONS TO TEST

- Prior to treatment with NSAIDS (esp. if expect long use)
- Patients with ITP
- Patients with unexplained Fe deficiency anemia
ACG guidelines state that if endoscopy used, first test of choice is urease test on antral biopsy.

Routine gastric histology: not necessary and expensive.

If urease test neg, then use histology, culture, noninvasive tests (breath, stool).

- Serology not reliably distinguish between active and past infection.
- One cost-saving measure: obtain but delay sending histology pending biopsy urease test.
BIOPSY UREASE TEST

- Sensitivity: 90-95% but specificity is 95-100%.
- False neg: recent GIB or with use of PPI, H2 blockers, antibiotics, or bismuth-containing compounds
- So neg. urease test in patients taking these above drugs does not rule out H pylori
  - Antisecretory Rx also interfere with histology so best to send serology
RAPID UREASE TEST

- Know patient’s H pylori status before leave endoscopy suite
  - Within one hour
  - Biopsy specimens sandwiched between reagent strip with pH indicator and pad containing urea.
  - One hour sensitivity and specificity: 89-98% and 89-93%
- Used commonly in Beijing Hospital
Historically hard to culture but techniques improving

Metronidazole resistance observed in 22-39% of isolates

Clarithromycin resistance in 11-12% isolates

Resistance to amoxicillin and tetracycline rare

Note, routine culture not recommended

But if refractory disease, may benefit
UREA BREATH TEST

- ACG: best nonendoscopic test for documenting H pylori infection
- Reasonable to confirm eradication of infection in all patients 4-6 weeks following treatment (esp. since cheap test)
- Sensitivity and specificity 88-95% and 95-100%
- Again, false neg. with antisecretory therapy, bismuth, or antibiotics
  - Patients should be off these meds at least 4 weeks and off PPI for at least 2 weeks
SEROLOGY

- Lab-based serology using ELISA to detect IgG or IgA inexpensive and well-suited to primary care
- But less sensitive and specific (90-100% and 76-96%)
- In young, symptomatic patients may be good alternative
  - Obviously depends on pretest probability of H pylori in population being studied
- Inaccurate tests common in elderly, cirrhotics
- Not useful for follow-up testing since many patients have antibodies for months-years post Rx
STOOL ANTIGEN

- Sensitivity and specificity: 94% and 86% in one study
- Same limitations of other tests using urease
OTHER DEVELOPING TESTS?

- $^{13}$C bicarbonate serologic assay using 2 serum specimens: one before meal and next 60 minutes after ingestion of $^{13}$C-urea rich meal
- PCR: only useful in detecting organism when ordinary culture difficult
- Salivary assay: oral cavity can be reservoir
- Urinary assay
A number of testing options are available including biopsy based (histology, rapid urease testing, culture, rapid polymerase testing), serology, 13C urea breath testing and stool antigen, however each test possess their individual advantage and disadvantage.

Once the diagnosis is established, multiple treatment regimens are available yet the optimal treatment regimen has not been established. We aim to review the treatment options in the management of *H. pylori* infection.

We will review the evidence behind triple therapy, quadruple therapy, sequential therapy and other therapeutic regimens in the eradication of this problematic disease.
STRONGLY RECOMMENDED INDICATIONS FOR H. PYLORI ERADICATION THERAPY

- Peptic ulcer disease – active or not including complicated ulcer
- Mucosa-associated lymphoid tissue lymphoma (MALToma)
- Atrophic gastritis
- Post-gastric cancer resection
- Patients who are first-degree relatives of gastric cancer patients
- Patients’ wishes – after full consultation with their physician
FACTORS INVOLVED IN CHOOSING TREATMENT REGIMENS

- Prevalence of Hp infection
- Prevalence of gastric cancer
- Resistance to antibiotics
- Cost level and available budget
- Availability of bismuth
- Availability of endoscopy, Hp tests
- Ethnicity
- Drug allergies and tolerance
- Previous treatments, outcome
- Effectiveness of local treatment
- Ease of administration
- Adverse effects
- Recommended dosages, treatment duration
TRIPLE THERAPY

- Standard dose twice daily Proton Pump Inhibitor (PPI)
  - Lansoprazole 30 mg
  - Omeprazole 20 mg
  - Pantoprazole
  - Rabeprazole 20 mg.

- Clarithromycin 500 mg twice daily and Amoxicillin 1,000 mg twice daily for a total of 7 to 14 days

- Recent data has suggested that this combination has lost efficacy with a maximum eradication rate of 70%

- Triple therapy should be considered a first line treatment if Clarithromycin resistance is less than 15% if more, alternative regimens should be considered
In patients with a Penicillin allergy, Metronidazole 500 mg twice daily can be used with comparable eradication rates (81%).

In patients who are unable to tolerate PPI therapy, a randomized control study of 101 patients suggests similar eradication rates with H2-receptor antagonists (86% in PPI group versus 94% in Nizatidine group, P = 0.3).
TRIPLE THERAPY

- A metaanalysis of 21 studies evaluating the eradication efficacy of prolonged treatment duration of standard triple therapy demonstrated a relative risk for eradication of 1.05 in 7-day treatment when compared to 10- day treatment.

- The same study demonstrated a relative risk for eradication of 1.07 for 7-day treatment compared to 14-day therapy; thereby suggesting that extending triple beyond seven days may not improve eradication response.
QUADRUPLE THERAPY

- Bismuth 525 mg four times daily, metronidazole 250 mg four times daily, tetracycline 500 mg four times daily and a standard dose PPI for a total of 7-14 days
- The eradication rate about 87%, some authors advocate bismuth based quadruple therapy as first line therapy for *H pylori*
- The first line treatment in areas of high clarithromycin resistance (> 15 percent) or in patients with a documented penicillin allergy
One limiting factor of quadruple therapy is the complexity of QID dosing and pill burden.

SE: Symptoms included: diarrhea, dyspepsia, nausea, abdominal pain, and taste perversion, changes in stool color or firmness and headache.
Twice daily PPI with Amoxicillin 1000 mg twice daily for five days, followed by PPI, Clarithromycin 500 mg twice daily and Tinidazole 500 mg twice daily for five days appears equally effective as quadruple therapy (93.3%).

In patients with a penicillin or clarithromycin allergy, Levofloxacin 250 mg twice daily can be substituted.
89% eradication rate in patients with Clarithromycin resistant strains

Still represents a reasonable first line regimen despite Clarithromycin resistance however in the presence of dual Clarithromycin and Metronidazole resistance, the eradication rate is significantly reduced to 33.3%

Very expensive
**CONCOMITANT THERAPY**

- Standard dose PPI, Amoxicillin 1000 mg twice daily, Clarithromycin 50 mg twice daily and Metronidazole 500 mg twice daily for 10-14 days

- It is similar to sequential therapy in terms of eradication with an eradication rate of 94% and maybe a simpler regimen when compared to sequential therapy as all antibiotics are given at once
A randomized trial comparing sequential and concomitant therapy, demonstrated comparable eradication rates (92.3% versus 93%, respectively) and similar adverse event rates (30.7% versus 26.9%).

A regimen consisting of: esomeprazole and amoxicillin for seven days then esomeprazole, amoxicillin, clarithromycin, and metronidazole for 7 seven days (sequential-concomitant hybrid therapy) generated a 99.1% eradication rate in 117 patients.
FLOUROQUINOLONES BASED THERAPY

- Levofloxacin 500 mg daily, Amoxicillin 1000 mg BID and standard dose PPI for a total ten days.

- The reported eradication rate is 87%

- A previous randomized control study comparing Levofloxacin 250 mg daily, omeprazole 40 mg daily Nitazoxanide 500 mg twice daily and Doxycycline 100 mg daily for 7 and 10 days (LOAD 7, LOAD 10) demonstrated 89.4% and 90% eradication rates respectively [35,36]
Levofloxacin may thus represent a reasonable treatment regimen in the setting of Clarithromycin resistance however the 2007 American College of Gastroenterology guidelines suggest that although these results are encouraging, further validation within the United States is warranted.
Non-endoscopic evaluation for the eradication of *H. pylori* is generally recommended 4 weeks after completion of therapy.

Urea breath test or a fecal antigen test is the most common tested used to ensure eradication.
About 20% of patients fail initial therapy.

A previous meta-analysis of 16 articles with a pooled analysis of 75 treatment arms indicated that re-treatment with PPI-based triple therapy or bismuth-based quadruple therapy carries a 69.8% and 75.8% re-eradication rate.
Re-treatment in a persistent *H. pylori* infection should avoid antibiotics that have been previously prescribed; i.e. if PPI based triple therapy was used as an initial therapy, bismuth based quadruple therapy or LOAD therapy should be considered.

A previous study by Dore et al suggests that the optimal salvage therapy should include: Omeprazole 20 mg, Tetracycline 500 mg, Metronidazole and Bismuth subcitrate 240 mg twice daily with mid and evening meals for 14 days as 93% of patients achieved eradication.
<table>
<thead>
<tr>
<th>Treatment</th>
<th>Days</th>
<th>No. of patients</th>
<th>Methods of evaluating eradication</th>
<th>Eradication rate % (ITT)</th>
<th>Eradication rate % (PP)</th>
<th>Adverse effects %</th>
<th>Ref.</th>
<th>Type of study</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low clarithromycin resistance area (&lt; 20%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPI (standard dose, bid) + amoxicillin (1 g, bid) + clarithromycin (500 mg, bid)</td>
<td>7-10</td>
<td>1975</td>
<td>UBT or H or R</td>
<td>Overall 77.3-100</td>
<td>0-33</td>
<td>Magraud et al[8]</td>
<td>Meta-analysis</td>
<td></td>
</tr>
<tr>
<td>PPI (standard dose, bid) + amoxicillin (1 g, bid) followed by a triple therapy with a PPI (standard dose, bid) + clarithromycin (500 mg, bid) + metronidazole/tinidazole (500 mg, bid)</td>
<td>5 + 5</td>
<td>5666</td>
<td>UBT or H or R</td>
<td>Overall 84.3</td>
<td>0-44</td>
<td>Gatta et al[9]</td>
<td>Meta-analysis</td>
<td></td>
</tr>
<tr>
<td><strong>High clarithromycin resistance area (&gt; 20%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPI (standard dose, bid) + amoxicillin (1 g, bid) + levofloxacin (500 mg, bid)</td>
<td>7-10</td>
<td>900</td>
<td>UBT or H or R</td>
<td>Overall 72-96</td>
<td>0-52</td>
<td>Bearnig et al[10]</td>
<td>Meta-analysis</td>
<td></td>
</tr>
<tr>
<td>PPI (standard dose, bid) + amoxicillin (1 g, bid) followed by a triple therapy with a PPI (standard dose, bid) + levofloxacin (250/500 mg, bid) + metronidazole (500 mg, bid).</td>
<td>5 + 5</td>
<td>250</td>
<td>UBT</td>
<td>96/96.8</td>
<td>98.3/98.4</td>
<td>22.1-23.5</td>
<td>Romano et al[6]</td>
<td>RCT</td>
</tr>
<tr>
<td>PPI (high dose, bid) + amoxicillin (1 g, bid) + levofloxacin (500 mg, bid) + metronidazole (500 mg, bid)</td>
<td>5</td>
<td>135</td>
<td>UBT</td>
<td>91.4</td>
<td>91.4</td>
<td>35.6</td>
<td>Kim et al[11]</td>
<td>RCT</td>
</tr>
<tr>
<td>PPI (high dose, bid) + amoxicillin (1 g, bid) + levofloxacin (500 mg, bid) + tinidazole (500 mg, bid)</td>
<td>5</td>
<td>90</td>
<td>UBT</td>
<td>92.2</td>
<td>96.5</td>
<td>27.3</td>
<td>Pederico et al[12]</td>
<td>RCT</td>
</tr>
<tr>
<td>PPI (standard dose, bid) + metronidazole (500 mg, bid) + bismuth (120 mg, q.i.d.) + tetracycline (500 mg, q.i.d.)</td>
<td>10</td>
<td>215</td>
<td>UBT</td>
<td>92</td>
<td>94</td>
<td>47</td>
<td>Malfertheiner et al[13]</td>
<td>RCT</td>
</tr>
<tr>
<td>PPI (high dose, bid) + amoxicillin (1 g, bid) followed by a quadruple therapy with a PPI (high dose, bid) + amoxicillin (1 g, bid) + clarithromycin (500 mg, bid) + metronidazole (500 mg, bid)</td>
<td>7 + 7</td>
<td>171</td>
<td>UBT</td>
<td>90</td>
<td>92</td>
<td>47</td>
<td>Molina-Infante et al[14]</td>
<td>RCT</td>
</tr>
</tbody>
</table>
SUMMARY

- *H. pylorus remains* a problematic and prevalent disease

- A number of treatment regimens are in the clinician’s arsenal however standard PPI based triple therapy and bismuth based quadruple therapy remain first line as the eradication rates remain relatively high (70-80%). The increase in clarithromycin resistance has led to the investigation of other therapeutic options including: Sequential therapy, Concomitant therapy and Levofloxacin based therapy as additional therapeutic regimens

- Confirming eradication is crucial and in the setting of persistent infection, bismuth based salvage therapy appears to represent a reasonable approach for salvage therapy.
Thank you