Aid Peptic Disease Revisited

IAGH Dec 2011
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DDRC/TUMS/Shariati Hospital
Peptic Ulcer is a Common Disease

- The annual incidence of active ulcer (GU & DU) in the U.S. is about 1.8% - 500,000 new cases per year.

- In addition, there are approximately 4 million ulcer recurrences yearly.
APD
Ulcers May Be Caused by Non-acid/peptic Disorders

Esophagus
- herpes simplex
- tablet induced tetracycline
- KCl
- others
- cytomegalovirus

Stomach
- carcinoma
- Kaposi’s
- lymphoma
- pancreatic rest
- syphilis
- candida

Duodenum
- Crohn’s disease
- pancreatic carcinoma
There are a number of myths surrounding the causes and treatment of ulcer disease:

- Spicy foods
- Alcohol
- Psychological stress
- Ulcer is an executive’s disease
- A bland diet heals ulcers
Helicobacter pylori
*H. pylori* is a causal factor in most cases of peptic ulcer disease

**Duodenal ulcer**
- 92% caused by *H. pylori*
- 2% caused by NSAID
- 1% caused by cancer (Zollinger Ellison)
- 5% caused by other factors

**Gastric ulcer**
- 70% caused by *H. pylori*
- 25% caused by NSAID
- 3% caused by cancer (Zollinger Ellison)
- 2% caused by other factors

Marshall 1994
Pathogenesis of Helicobacter pylori-positive duodenal ulcer

- **Somatostatin ↓**
- **Gastrin ↑**
- **Acid secretion ↑**

- **H. pylori infection**
  - **H. pylori gastritis**

- **Defect:**
  - Bicarbonate secretion
  - Clearance of bulbar acidity

- **Gastric metaplasia in duodenum**

- **Duodenitis**

- **Facultative factors**
  - (stress, smoking)

- **Mucosal barrier breakdown**

- **Virulence factors**
  - CagA
  - VacA
  - Other: IceA, OiPA, BabA

- **Duodenal ulcer**
Antrum-predominant HP infection gastritis Phenotype typically seen in patients with duodenal ulcer.
*H. pylori* Alters Control of Gastric Secretion by Decreasing Somatostatin Release

**No* H. p.* Infection**

- D (Somatostatin cell) → G (Gastrin cell) → PC (Parietal cell)
- GRP (Gastrin Releasing Peptide)

**H. p. Infected**

- D (Somatostatin cell) → G (Gastrin cell) → PC (Parietal cell)
- GRP (Gastrin Releasing Peptide)

D – Somatostatin cell
G – Gastrin cell
PC – Parietal cell
GRP – Gastrin Releasing Peptide
NSAID the second most common cause of APD

Gastric acid plays a central role in NSAID-associated gastroduodenal damage

- **PROTECTIVE FACTORS**
  - Mucus layer
  - Ionic gradient
  - Bicarbonate layer
  - Prostaglandins
  - Surface epithelial cells
  - Mucosal blood supply

- **AGGRESSIVE FACTORS**
  - Aspirin and other NSAIDs
  - Gastric acid
  - Pepsin
  - H. pylori

Neutral environment → Acidic environment
Main environmental risk factors of duodenal ulcer in residents of Ardabil province; result of final stage step of logistic regression analysis

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>H. pylori infection</td>
<td>positive vs. negative</td>
<td>5.6 (1.9 – 8.8)</td>
</tr>
<tr>
<td>Smoking</td>
<td>Current vs. non</td>
<td>2.3 (1.4 – 6.5)</td>
</tr>
<tr>
<td>Gender</td>
<td>Men vs. women</td>
<td>3.6 (1.2 – 5.8)</td>
</tr>
<tr>
<td>Residence</td>
<td>Urban vs. Rural areas</td>
<td>1.9 (1.1 – 5.2)</td>
</tr>
</tbody>
</table>
Main environmental risk factors of gastric ulcer in residents of Ardabil province; result of final stage step of logistic regression analysis

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>OR (95 % CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>H.pylori infection</td>
<td>3.1 (2.1 – 4.7)</td>
<td>0.002</td>
</tr>
<tr>
<td>Smoking</td>
<td>1.8 (1.1 – 6.8)</td>
<td>0.034</td>
</tr>
<tr>
<td>Chronic NSAID intake</td>
<td>2.8 (1.3 – 4.4)</td>
<td>0.019</td>
</tr>
</tbody>
</table>
## Prevalence of APD Population based studies

<table>
<thead>
<tr>
<th>Authors</th>
<th>Countries</th>
<th>% of DU</th>
<th>% of GU</th>
<th>% of APD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li et al AJG 2010</td>
<td>China Shanghi</td>
<td>13.3</td>
<td>6.1</td>
<td>17.2</td>
</tr>
<tr>
<td>Malekzadeh et al, JCP 2004</td>
<td>Iran Ardabil</td>
<td>4.94</td>
<td>3.26</td>
<td>8.2</td>
</tr>
<tr>
<td>Zagari et al AJG 2010</td>
<td>Europe</td>
<td>3.9</td>
<td>2.3</td>
<td>6.2</td>
</tr>
</tbody>
</table>
APD Burden in Iran

- PUD is still common in Iran and largely asymptomatic.
- This in turn suggests that up to one quarter of individuals with PUD may go on to develop peptic ulcer bleeding without showing any related symptoms.
- If these rates are extrapolated to the total population of Iran (70 million), then it can be estimated that we have about 560,000 APD in the country among them 350,000 individuals will have DU and 210,000 GU.
## Prevalence of APD in Tehran Dyspeptic Population 2011

<table>
<thead>
<tr>
<th>Authors</th>
<th>Sample size</th>
<th>% of DU</th>
<th>% of GU</th>
<th>% of APD</th>
<th>% GERD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Khademi et al</td>
<td>2847</td>
<td>13.8</td>
<td>1.0</td>
<td>14.80</td>
<td>72.5</td>
</tr>
<tr>
<td>In Press 2012</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Most Common Digestive Disease Discharge Diagnosis in Shariati Hospital Tehran (2000-2009)

<table>
<thead>
<tr>
<th></th>
<th>Diagnosis</th>
<th>ICD 10 Code</th>
<th>Male</th>
<th>Female</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>HBV Induced Liver Cirrhosis</td>
<td>K74(B18.1)</td>
<td>529</td>
<td>118</td>
<td>647 (15.83 %)</td>
</tr>
<tr>
<td>2</td>
<td>Cryptogenic Cirrhosis</td>
<td>K74.6</td>
<td>291</td>
<td>158</td>
<td>449 (10.99 %)</td>
</tr>
<tr>
<td>3</td>
<td>CBD Stone</td>
<td>K80.5</td>
<td>182</td>
<td>177</td>
<td>359 (8.78 %)</td>
</tr>
<tr>
<td>4</td>
<td>GI Bleeding</td>
<td>K92.2</td>
<td>259</td>
<td>94</td>
<td>353 (8.63 %)</td>
</tr>
<tr>
<td>5</td>
<td>AIH induced Liver Cirrhosis</td>
<td>K75.4</td>
<td>90</td>
<td>170</td>
<td>260 (6.36 %)</td>
</tr>
<tr>
<td>6</td>
<td>HCV induced Liver Cirrhosis</td>
<td>K74(B18.2)</td>
<td>201</td>
<td>48</td>
<td>249 (6.09 %)</td>
</tr>
<tr>
<td>7</td>
<td>Acute Cholangitis</td>
<td>K83</td>
<td>128</td>
<td>91</td>
<td>219 (5.35 %)</td>
</tr>
<tr>
<td>8</td>
<td>Cholangiocarcinoma</td>
<td>C22.1</td>
<td>119</td>
<td>54</td>
<td>173 (4.23 %)</td>
</tr>
<tr>
<td>9</td>
<td>Gastric Cancer</td>
<td>C16</td>
<td>118</td>
<td>46</td>
<td>164 (4.01 %)</td>
</tr>
<tr>
<td>10</td>
<td>Ulcerative Colitis</td>
<td>K51</td>
<td>78</td>
<td>85</td>
<td>163 (3.99 %)</td>
</tr>
<tr>
<td>11</td>
<td>Duodenal Ulcer</td>
<td>K26</td>
<td>125</td>
<td>30</td>
<td>155 (3.79 %)</td>
</tr>
<tr>
<td>12</td>
<td>Acute Pancreatitis</td>
<td>K85</td>
<td>75</td>
<td>77</td>
<td>152 (3.71 %)</td>
</tr>
<tr>
<td>13</td>
<td>Pancreatic Cancer</td>
<td>C25</td>
<td>88</td>
<td>47</td>
<td>135 (3.30 %)</td>
</tr>
<tr>
<td>14</td>
<td>Gastric Ulcer</td>
<td>K25</td>
<td>90</td>
<td>27</td>
<td>117</td>
</tr>
</tbody>
</table>
## Digestive Diseases during 2000-2009 in Shariati Hospital, Tehran, Iran

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>ICD 10 Code</th>
<th>2000-2004 Number (%)</th>
<th>2005-2009 Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 CIRRHOSIS BASED ON HBV</td>
<td>K74(B18.1)</td>
<td>393 (21.73)</td>
<td>254 (11.15)</td>
</tr>
<tr>
<td>2 Cryptogenic Cirrhosis</td>
<td>K74.6</td>
<td>210 (11.60)</td>
<td>239 (10.49)</td>
</tr>
<tr>
<td>3 CBD Stone</td>
<td>K80.5</td>
<td>126 (6.96)</td>
<td>233 (10.22)</td>
</tr>
<tr>
<td>4 GI Bleeding</td>
<td>K92.2</td>
<td>149 (8.23)</td>
<td>204 (8.95)</td>
</tr>
<tr>
<td>5 Cirrhosis based on AIH</td>
<td>K75.4</td>
<td>124 (6.85)</td>
<td>136 (5.97)</td>
</tr>
<tr>
<td>6 Cirrhosis based on HCV</td>
<td>K74(B18.2)</td>
<td>112 (6.19)</td>
<td>137 (6.01)</td>
</tr>
<tr>
<td>7 Cholangitis</td>
<td>K83</td>
<td>61 (3.37)</td>
<td>158 (6.93)</td>
</tr>
<tr>
<td>8 Cholangiocarcinoma</td>
<td>C22.1</td>
<td>59 (3.26)</td>
<td>114 (5)</td>
</tr>
<tr>
<td>10 Ulcerative Colitis</td>
<td>K51</td>
<td>73 (4.03)</td>
<td>90 (3.95)</td>
</tr>
<tr>
<td>11 Duodenal Ulcer</td>
<td>K26</td>
<td>79 (4.36)</td>
<td>76 (3.33)</td>
</tr>
<tr>
<td>12 Acute Pancreatitis</td>
<td>K85</td>
<td>46 (2.54)</td>
<td>106 (4.65)</td>
</tr>
<tr>
<td>13 Pancreatic Cancer</td>
<td>C25</td>
<td>31 (1.71)</td>
<td>104 (4.56)</td>
</tr>
<tr>
<td>14 Gastric Ulcer</td>
<td>K25</td>
<td>65 (3.59)</td>
<td>52 (2.28)</td>
</tr>
</tbody>
</table>
Time trends of gastro-esophageal reflux disease (GERD) and peptic ulcer disease (PUD) in Dyspeptic patient in Tehran

Percentage of GERD, DU, GU, Positive Urease test, and normal subjects in each year of endoscopy

Year of Endoscopy

Percentage
0.0%
10.0%
20.0%
30.0%
40.0%
50.0%
60.0%
70.0%
80.0%
90.0%


GERD
GU
DU
Normal
Positive Urease Test

Sepanlue, Malekzadeh MEJDD 2011
Common diagnosis for GI disorders in outpatient clinic

<table>
<thead>
<tr>
<th></th>
<th>Diagnosis</th>
<th>Count</th>
<th>Percentage</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>GERD</td>
<td>2620</td>
<td>32%</td>
<td>K21</td>
</tr>
<tr>
<td>2</td>
<td>IBS</td>
<td>2022</td>
<td>25%</td>
<td>K58</td>
</tr>
<tr>
<td>3</td>
<td>DU</td>
<td>1130</td>
<td>14%</td>
<td>K26</td>
</tr>
<tr>
<td>4</td>
<td>Dyspepsia</td>
<td>909</td>
<td>11%</td>
<td>K30</td>
</tr>
<tr>
<td>5</td>
<td>CHB</td>
<td>581</td>
<td>7%</td>
<td>B18.0</td>
</tr>
<tr>
<td>6</td>
<td>UC</td>
<td>365</td>
<td>4%</td>
<td>K51</td>
</tr>
<tr>
<td>7</td>
<td>Cirrhosis</td>
<td>331</td>
<td>4%</td>
<td>K74</td>
</tr>
<tr>
<td>8</td>
<td>Gastrodeodenitis</td>
<td>275</td>
<td>3%</td>
<td>K29</td>
</tr>
<tr>
<td>9</td>
<td>NAFLD</td>
<td>231</td>
<td>3%</td>
<td>K76</td>
</tr>
<tr>
<td>10</td>
<td>Crohn’s</td>
<td>207</td>
<td>2%</td>
<td>K50</td>
</tr>
</tbody>
</table>
Time trends of standardized cohort mortality ratio of gas GU & DU
Age-adjusted death rates from gastric and duodenal ulcer in different countries.
Birth-cohort analysis of gastric ulcer mortality in Japan
Declining APD in ASIA

• Mortality from gastric and duodenal ulcer has decreased in the developed countries of Asia and South America similarly to in Europe and in North America.

• The time trends of ulcer mortality were shaped by underlying birth-cohort patterns that are identical to the ones found in European countries, Canada, and the United States.

• The ubiquitous decline in ulcer mortality of peptic ulcer in countries from different parts of the world is likely to be associated with a worldwide decline in the occurrence of H. pylori infection.
Gastric acid secretion
Evolution
Importance
Most sophisticated, energetically expensive biological function

• Gastric acid secretion is one of the most sophisticated, energetically expensive and highly developed biological functions.

• Creating and sustaining a H+ conc. gradient of more than 1,000,000 : 1 across the gastric epithelium.

• *Parietal cells are full of mitochondria that generate the (ATP) required to drive the proton pump.*
Gastric acid is potentially dangerous

- The production of gastric acid by the stomach is potentially dangerous.
- The acidic gastric juice and proteolytic enzymes are able to digest human tissue.
Gastric acid secretion is highly conserved

• Gastric secretions are separated from the rest of the body by an epithelium that is only a single cell thick.

• For that reason, there is a very complex system for controlling acid secretion and protecting the epithelium.
Gastric Acid Secretion

Highly Conserved

From appearance of land-roaming creatures (vertebrates) 350 million years ago
Gastric acid has a number of recognized functions

- Initiation of protein digestion,
- Denaturation of potentially immunogenic proteins,
- Facilitation of absorption of iron, calcium, and vitamin B12.
- Killing of potentially pathogenic ingested microorganisms.
killing of potentially pathogenic microorganisms

• The only recognized functions of acid that could justify the energy and risks associated with secreting gastric acid is the killing of potentially pathogenic microorganisms.

• Is this original critical function still relevant today, or has it become redundant?
Changes in the human environment 20,000 years ago

• 20,000 years ago, humans learned how to control fire and started using it for cooking, and in this way reduced the risk of ingesting contaminated flesh.
2000 years ago,

• Approximately 2000 years ago, the first sewage systems and clean drinking water appeared in parts of the Roman Empire and have now become standard throughout the developed world.
Fifty years ago

• Fifty years ago, food refrigeration appeared, with further improvement in food safety.
Over the last 25 years

- The production of food and its storage have become much more stringent and free from pathogenic contamination.
Survival in a very sterile environment

• A progressive and probably exponential decrease in human exposure to potentially pathogenic microorganisms over recent times.
• Gastric acid secretion evolved to allow survival in a very different environment from the relatively sterile one that now characterizes the western world
Gastric acid secretion is less important in the present sterile environment

- A number of observations do suggest that acid secretion is redundant and no longer required for life in the developed world.
- Marked long-term suppression of gastric acid with proton-pump inhibitors rarely causes infective complications.
Gastric acid secretion is certainly less important today!

- Patients who develop auto-immune atrophic gastritis and associated complete achlorhydria rarely have problems, provided they receive the necessary vitamin B12 supplements.

- Gastric acid secretion is certainly less important in the environment of the western world than it has been in the past.
H. pylori

• H. pylori has colonized the human stomach since at least the time our ancestors migrated from Africa 65,000 years ago ..
Evidence for long and intimate association between humans and *H. pylori* infection

*H. Pylori* travelled in humans out of Africa ~ 65,000 years ago

(Linz et al. Nature 2007;445:915-918)
Gastric HP infection Phenotypes

• Various clinical and epidemiologic studies have suggested that peptic ulcer occurs preferentially in subjects who contract the disease during childhood or adolescence.

• While early acquisition of H. pylori shortly after birth is primarily associated with pangastritis and gastric cancer, first acquisition of this infection during childhood and adolescence is more likely to result in gastric and duodenal ulcer, respectively.
Diminution in acid secretion with increasing age

- Diminution in acid secretion with increasing age has therefore been a feature of the stomach since as long ago as we know.
Maximal Acid Output (mmol/h) - decreases with age

- CagA - ve (n = 57)
- CagA + ve (n = 70)

P < 0.01

(Derakhshian et al. J.Clin.Path. 2006;59;1293-1299)
Acid secretion is maintained throughout life

• The very recent disappearance of H. pylori infection means that acid secretion is maintained throughout life and is thus now substantially higher in adults than it was in previous generations
Environmental changes that have made acid secretion less important

• Previously, when everyone was infected with H. pylori, there was progressive damage to the gastric mucosa with increasing age and a progressive decrease in acid-secreting capacity.

• Nowadays, the stomach retains its capacity to secrete acid into old age, and that capacity may even increase as one gets older.
Balance between the acid we need to protect us from bacteria and the amount of acid we are producing.

- Profound change in the balance between the amount of acid we need to protect us from bacteria and the amount of acid we are producing.
Acid secretion has increased but our need for acid has decreased

• Our acid secretion has increased, while our need for acid has actually decreased.

• Never before in the history of human–microbial conflict has so much acid been produced by so many humans to kill so few bacteria
Evidence for the recent increase in acid secretion being potentially damaging

- Studies of the effect of proton-pump inhibitor therapy. reduces gastric acid secretion during treatment, it also results in a marked rebound acid hypersecretion following discontinuation of treatment.
GERD appeared

- Consequently, for a month or more after discontinuing such therapy, acid secretory capacity is approximately 50% more than it was prior to starting the treatment.

- This increase in acid secretion is associated with development of new-onset upper gastrointestinal symptoms, such as GERD.
Physiological volumes of GERD become pathological

• An increase in gastric acidity can make previous physiological volumes of GERD become pathological.

• High prevalence of GERD and its complications and also the significant proportion of the population now taking PPI.
PPI instead of H.pylori

• As HP infection rate decline we need to control acid by PPI
• Is this a good price to pay!? 
**Divergent Responses to *H. pylori* Infection**

**Chronic *H. pylori* infection**

- **Duodenal ulcer phenotype**
  - Around 10-15% of infected subjects
  - Antral predominant Gastritis
  - High gastrin and acid secretion
  - Impaired inhibitory control of acid secretion
  - Protection from gastric cancer

- **Simple gastritis phenotype**
  - Majority of infected subjects
  - Mild mixed gastritis
  - High gastrin but normal acid secretion
  - No gastric atrophy
  - No significant clinical outcome

- **Gastric cancer phenotype**
  - Around 1% of infected subjects
  - Corpus-predominant gastritis
  - Multi-focal atrophic gastritis
  - High gastrin
  - Hypo/achlorhydria
  - Low pepsinogen I and pepsinogen I/II ratio
  - Increased risk of gastric cancer

*Amieva & El-Omar Gastroenterology 2008*
Trend Of Incidence

![Graph showing trends of incidence over time for different conditions.](image-url)
Serological predictors of gastric cancer

- Positive *H. pylori* serology including CagA
- Surrogate markers of gastric atrophy: PG I and PG I/II ratio
There are differences in CagA among US/European *H. pylori* strains.
H. Pylori Neonatal Vaccination

• We should still wait for an effective vaccine
Safety and Immunogenicity of an Intramuscular Helicobacter pylori Vaccine in Noninfected Volunteers: A Phase I Study

PETER MALFERTHEINER et al
*Otto-von-Guericke Universitaet, Magdeburg, Germany; ‡Novartis Vaccines, Marburg, Germany;
GASTROENTEROLOGY 2008;135:787–795
Aim

- *We* sought to study the safety and immunogenicity of a vaccine consisting of recombinant VacA, Cag A, and NAP given intramuscularly with aluminium hydroxide as an adjuvant to noninfected healthy subjects.
HP3 Vaccine

- consisted of sterile purified recombinant VacA, CagA, and NAP adsorbed onto aluminium hydroxide (1 mg/mL), in 0.5 of isotonic buffer contained in prefilled syringes for IM injection into the deltoid muscle.

- Antigens were expressed in *E coli* as full-length proteins and exhibited 95% purity after appropriate chromatographic steps as previously described.

- Formulations containing low (10 g) or high (25 g) doses of the 3 antigens were tested.
After 40 years

infection we will have gastric cancer in already infected subjects for the next 40 years.

• Each year the curve would move further to the right such that by approximately 40 years gastric cancer would be a very rare disease
Two pronged approach

• Eradication
• Targeted surveillance.
One Goal of Ulcer Surgery is to Prevent Vagal-Stimulated Gastric Acid Secretion

Normal

Vagotomy & Pyloroplasty

Vagotomy & Antrectomy

- Vagotomy decreases peak H+ output by approximately 50%
- Vagotomy *plus* antrectomy decreases peak H+ output by approximately 85%
Gastric Resections Markedly Decrease or Eliminate Gastric Acid Secretion

Vagotomy & Billroth I  Vagotomy & Billroth II  Total Gastrectomy

- Total gastrectomy eliminates all gastric acid secretion
• Screening and surveillance programmes, as adopted in Japan, have generally resulted in a reduction in cancer mortality among the population screened but are costly and inefficient.

• It is possible to increase the yield of APD & cancer within the screened population by focusing on those with atrophy identified by abnormal serum pepsinogen levels.
in determining the risk of imminent development of gastric cancer and that detecting atrophic gastritis by serum pepsinogens is the important test.
Cancer prone phenotype
Individualized Therapy

- Patients with H pylori infection but no evidence of atrophy had a similar cancer risk to those with an uninfected healthy stomach, at least over the subsequent five years examined in this study.
Individualized Therapy

Screen for pepsinogen I&II

Normal PEP I & PEP II

Benign Phenotype

No therapy
Identification of phenotypes
Individualized Therapy

Screen for pepsinogen I&II

Elevated P11

Cancer phenotype

HP eradication
Screening HP infected Subjects

a cancer prone phenotype

Screen for pepsinogen I&II

Low pepsinogen I (Cancer prone phenotype)

HP eradication & Surveillance UGIE

Early detection of Cancer