The Epidemiology & Prevention of Gastric Cancer in the Americas

Douglas Morgan, MD MPH FACG
Vanderbilt University
Health Disparities in Cancer Prevention & Diagnosis
UPR Comprehensive Cancer Center
National Cancer Institute
April 12, 2013
General Overview

• Gastric cancer epidemiology
  - Global impact
  - North America: Disparities
  - Latin America: The Altitude Enigma

• Gastric cancer prevention
  - H. pylori eradication initiatives
  - Guidelines for surveillance of precancerous lesions
  - Evolution of imaging and resection modalities
  - Innovation in infrastructure for cancer prevention
Inflammation and Cancer: 16% (23% vs 7.4%)
demartel, lancet onc 2012

- Gastric cancer, *H. pylori*
- Hepatocellular cancer, HBV & HCV
- Cervical cancer, HPV
- Nasopharyngeal carcinoma, EBV
- Bladder cancer, Schistosomiasis

- Esophageal cancer, Esophagitis
- Pancreatic cancer, Chronic pancreatitis
- Colon cancer, Inflammatory bowel disease
Gastric cancer: Core Epidemiology

**Leading cause** of infection-associated cancer mortality

*H. pylori* is a WHO Class I Carcinogen

**Second** leading cause of cancer mortality

Annual incidence over one million

All-cause mortality worldwide: 14th

Will rise to 10th, given growing & aging populations

Consistent 2:1 male to female ratio

Significant **geographic variability** offers the opportunity for scientific discovery & focused intervention

High incidence regions include:

Latin America, Eastern Asia, Eastern Europe
Components of Cancer Death Trends 2002-2030
Greenberg R, Merida HP GC Symposium 2010

The graph illustrates the components of cancer death trends from 2002 to 2030. It shows the total change in cancer deaths (black bars), population growth (white squares), population ageing (white triangles), and epidemiological change (diagonal bars). The graph highlights the significant contribution of deaths from lung cancer and stomach, colon, and rectum compared to deaths from breast, cervix, uterus, and ovary. Prostate cancer deaths show a relatively small contribution in the graph.
Noncardia Gastric Cancer Age-Specific Incidence Rates: Whites

Anderson, W. F. et al. JAMA 2010;303:1723-1728
Noncardia Gastric Cancer Age-Specific Incidence Rates: Whites

Anderson, W. F. et al. JAMA 2010;303:1723-1728
U.S. Gastric Cancer Incidence by Race & Ethnicity
Siegel R, CaJC 2012; Morgan DR, AGA Perspectives; IARC 2010

- **CAUCASIAN**
  - Male: 8.5
  - Female: 4.0

- **AMERICAN INDIAN***
  - Male: 13.9
  - Female: 6.8

- **HISPANIC/LATINO**
  - Male: 13.8
  - Female: 8.4

- **AFRICAN AMERICAN**
  - Male: 16.4
  - Female: 8.2

- **ASIAN AMERICAN**
  - Male: 16.8
  - Female: 9.4

* Includes Alaska natives
** Includes Pacific Islanders
Pacific Rim of Fire → Gastric cancer
Gastric Cancer Mortality in the Americas
IARC GLOBOCAN 2010; Torres J, Cancer Causes Control 2013
MesoAmerican topography
GC Mortality Regional Variation, México 2008

Tumor maligno del estómago

- Chiapas: 8.05
- Yucatán: 7.96
- Morelos: 7.04
- Guerrero: 7.03
- Campeche: 6.61
- Oaxaca: 6.56

*Tasa por 100 000 habitantes

Subdirección de Geografía Médica y Sistemas / CENIDSP / INSP
Heterogeneidad Regional y Comunal en RR CG

RR of Gastric Cancer by Region

ENS2003
“Correa-gram”: Gastric Cancer Pathway

Non-colonized mucosa → Superficial gastritis → Atrophic gastritis → Intestinal metaplasia → Dysplasia → Gastric adenocarcinoma

Molecular genetic aberration: TP53 mutation Incidence: (30-50%)

RAS mutation (10%) Loss of DCC (20-60%)

Pathogenesis Triangle for Gastric Cancer

Host Genetic Factors
Cytokine polymorphisms (IL1B, IL-10, TNFα)

H. Pylori
Virulence factors (cagA, vacA, babA2)

Environmental Factors
Diet: Antioxidants & Insults
Co-infections: EBV
Other: Tobacco, Alcohol

Gastritis
Atrophy
Intestinal metaplasia
Dysplasia
Adenocarcinoma
Honduras: Gastric Cancer Initiative
Honduras: Gastric Cancer Initiative
Honduras, Hospital de Occidente
• Incidence 2000-09, mean ASRs:
  ➢ Males 30.8 (25-40), Females 13.9 (9.4-23)

• Patient population
  ➢ Male : Female ratio, 2.1 : 1
  ➢ Median age: 58 (youngest patient, 17)
  ➢ Age distribution: <45 10%<55 25%

• Endoscopy yield: 1 cancer / 5.1 endoscopies
  ➢ Pyloric obstruction: 35.2% with high mortality

• Pathology: 56% diffuse, 34% intestinal, 10% indeterminate
Gastric Cancer and the High Combination Prevalence of Host Cytokine Genotypes and *Helicobacter pylori* in Honduras

DOUGLAS R. MORGAN,* RICARDO L. DOMINGUEZ,** TEMITOPE O. KEKU,* PARIS E. HEIDT,* CHRISTOPHER F. MARTIN,* JOSEPH A. GALANKO,* OLUWASEUN A. OMOFOYE,* and ROBERT S. SANDLER*

---

**Table 3. Cytokine Allele Frequencies Among Cases and Controls in Honduras**

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Genotype</th>
<th>Controls (n = 162)</th>
<th>Cases (n = 170)</th>
<th>Odds ratio (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IL-1β-511</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genotype</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CC</td>
<td></td>
<td>30 (18%)</td>
<td>39 (23%)</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td>CT</td>
<td></td>
<td>92 (57%)</td>
<td>73 (43%)</td>
<td>.6 (.3–1.1)</td>
</tr>
<tr>
<td>TT</td>
<td></td>
<td>40 (25%)</td>
<td>58 (34%)</td>
<td>1.1 (.6–2.1)</td>
</tr>
<tr>
<td>CT + TT</td>
<td></td>
<td>132 (82%)</td>
<td>131 (77%)</td>
<td>.8 (.4–1.3)</td>
</tr>
<tr>
<td>Allele</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td></td>
<td>152 (94%)</td>
<td>151 (44%)</td>
<td></td>
</tr>
<tr>
<td>T</td>
<td></td>
<td>172 (53%)</td>
<td>189 (56%)</td>
<td></td>
</tr>
<tr>
<td><strong>IL-10-1082</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genotype</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GG</td>
<td></td>
<td>11 (7%)</td>
<td>7 (4%)</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td>AG</td>
<td></td>
<td>49 (30%)</td>
<td>42 (25%)</td>
<td>1.3 (.5–3.8)</td>
</tr>
<tr>
<td>AA</td>
<td></td>
<td>104 (63%)</td>
<td>121 (71%)</td>
<td>1.9 (.7–5.0)</td>
</tr>
<tr>
<td>AG + AA</td>
<td></td>
<td>150 (92%)</td>
<td>163 (96%)</td>
<td>1.7 (.6–4.5)</td>
</tr>
<tr>
<td>Allele</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td></td>
<td>254 (78%)</td>
<td>284 (84%)</td>
<td></td>
</tr>
<tr>
<td>G</td>
<td></td>
<td>71 (22%)</td>
<td>56 (16%)</td>
<td></td>
</tr>
<tr>
<td><strong>TNFα-308</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genotype</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GG</td>
<td></td>
<td>149 (93%)</td>
<td>151 (90%)</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td>AG</td>
<td></td>
<td>12 (7%)</td>
<td>17 (10%)</td>
<td>1.4 (.65–3.0)</td>
</tr>
<tr>
<td>AA</td>
<td></td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Allele</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G</td>
<td></td>
<td>245 (95%)</td>
<td>319 (93%)</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td></td>
<td>12 (4%)</td>
<td>17 (5%)</td>
<td></td>
</tr>
<tr>
<td><strong>IL-1RN</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genotype</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LL</td>
<td></td>
<td>56 (72%)</td>
<td>38 (54%)</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td>L2</td>
<td></td>
<td>13 (17%)</td>
<td>22 (31%)</td>
<td>2.5 (1.1–5.6)</td>
</tr>
<tr>
<td>22</td>
<td></td>
<td>9 (11%)</td>
<td>11 (15%)</td>
<td>1.8 (.7–4.8)</td>
</tr>
<tr>
<td>Allele</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L</td>
<td></td>
<td>125 (80%)</td>
<td>98 (65%)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>31 (20%)</td>
<td>44 (31%)</td>
<td></td>
</tr>
</tbody>
</table>
# H. pylori Virulence Genes

Romano M, NCPGH 2006; Peek RM, Nature Rev 2002

<table>
<thead>
<tr>
<th>Genetic locus</th>
<th>cag island</th>
<th>vacA</th>
<th>babA2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Conservation between strains</strong></td>
<td>60–70% Western strains</td>
<td>Always present, alleles vary</td>
<td>~85%</td>
</tr>
<tr>
<td><strong>Function</strong></td>
<td>Forms scaffold apparatus that allows bacterial protein(s) to enter host epithelial cells</td>
<td>?</td>
<td>Bacterial adhesion to cell surface</td>
</tr>
<tr>
<td><strong>Epidemiological disease association</strong></td>
<td>Peptic ulcer disease, gastric cancer</td>
<td>Peptic ulcer disease, gastric cancer</td>
<td>Peptic ulcer disease, gastric cancer</td>
</tr>
<tr>
<td><strong>Genotype associated with disease</strong></td>
<td>cagA⁺</td>
<td>vacAs1m1</td>
<td>babA2⁺</td>
</tr>
</tbody>
</table>


H. Pylori: Phylogenetics

Covacci et al, Science 1999 284: 1328-1333
Colombia: MLST analysis of 64 cagA+ vacA s1m1 Hp strains
de Sablet, Gut 2011

A

B


<table>
<thead>
<tr>
<th></th>
<th>Low Risk Region</th>
<th>High Risk Region</th>
</tr>
</thead>
<tbody>
<tr>
<td>hpAfrica1</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td>hpEurope</td>
<td>10</td>
<td>35</td>
</tr>
<tr>
<td>Fisher’s exact test</td>
<td>p&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

©2011 by BMJ Publishing Group Ltd and British Society of Gastroenterology
Colombia: Histopathological analysis of Hp strains

de Sablet, Gut 2011

A

\[ \text{Histopathology score} \]

<table>
<thead>
<tr>
<th>hpAfrica1</th>
<th>hpEurope Low Risk Region</th>
<th>hpEurope High Risk Region</th>
</tr>
</thead>
</table>

\[ p=0.002 \]

\[ p=0.032 \]

B

de Sablet T et al. Gut doi:10.1136/gut.2010.234468

©2011 by BMJ Publishing Group Ltd and British Society of Gastroenterology
Dietary Selenium in Colombia
Pathogenesis Triangle: Honduras

**Host Genetic Factors**
- IL-1B-511T* 82%
- IL-10-1082* 93%
- TNFa-308A* 7%

**H. Pylori**
- Population: 85%
- CagA: 84%

**Environmental Factors**
- Diet: +Salt, -Selenium
- Co-infections: EBV

**Pathology**
- Gastritis
- Atrophy
- Intestinal metaplasia
- Dysplasia
- Adenocarcinoma
Gastric Cancer Prevention Program

Diet and Nutrition

HP Eradication (age<40, <IM)

Endoscopy Surveillance (age>40, >IM)

Education Supplements

Risk populations

Risk populations

Antioxidants

Intervention

Screening Program
Gastric Cancer Prevention Program

Diet and Nutrition

HP Eradication (age<40, <IM)

Education Supplements

Pilot Study

Endoscopy Surveillance (age>40, >IM)

Risk populations

Antioxidants

Intervention

Screening Program
Latin America *H. pylori* and Gastric Cancer Study Group

**Goal:** Reduction of gastric cancer morbidity and mortality in Latin America

**Consortium Aims, 2009-12:**
- Optimize *H. pylori* eradication regimens
- Post-treatment & One-year outcomes
- Biomarker evaluation for *H. pylori* and GC
- Capacity building for cancer prevention

**Funding:** Bill and Melinda Gates Foundation

**Study management:**
- Southwest Oncology Group (SWOG)

Greenberg ER, Lancet 2011
Morgan DR, JAMA 2013
Latin America Trial Sites

México, northern & southern
Ciudad Obregón, Sonora
Tapachula, Chiapas

Honduras, Copán
Western Regional Hospital

Nicaragua, León
University of Nicaragua, León

Costa Rica, Guanacaste
INCIENSA Fundación

Colombia, Pasto
Universidad de Valle

Chile, Santiago
Pontificia Universidad Católica
Trial Design Principles

• Public health approach: prevention of gastric cancer
• Diverse Latin American populations
• Non-invasive diagnosis of *H. pylori* infection (UBT)
• Use of quality generic medications in each country
• Limited medication compliance measures
• Retreatment was voluntary for study subjects
• Community-based sampling
Community-based Recruitment
**H. pylori** Treatment Regimens

**Initial randomized treatment**
- PPI, bid, lansoprazole 30mg

**Triple therapy**, bid, 14 days (PAC-14)
- PPI, amoxicillin 1gm, clarithromycin 500mg

**Sequential therapy**, bid, 5 + 5 days (SEQ-10), hypothesis
- PPI, amoxicillin 1gm
- PPI, clarithromycin 500mg, metronidazole 500mg

**Concomitant therapy**, bid, 5 days (PACM-5)
- PPI, amoxicillin 1gm, clarithromycin 500mg, metronidazole 500mg

**Retreatment regimen**
**Quadruple therapy**, qid, 14 days (PBMT-14), voluntary
- PPI bid, bismuth 524mg, metronidazole 500mg, tetracycline 500mg
Study Schema

Community-based recruitment (n=1859)

13C Urea Breath Test (79% positive)

Randomization (n=1463)

- Triple
- Sequential
- Concomitant

6-8 weeks: UBT + evaluation (n=1414)

- Hp positive
- Hp negative
- Hp unknown

Quadruple

1 year: UBT + evaluation (n=1340)
Study Population Characteristics

- Healthy subjects recruited from community populations
- Study site balance: 14-15% from each site
- Age: 58% were over age 40
- Gender: 59% were women
- Education: 47% with less than a high school education
- Symptoms: 26% had chronic dyspepsia (Rome III criteria)
- *H. pylori* positive: 79% (CagA positive 84.8%)
- Substance use: alcohol 7.7%, tobacco 16%
Community-based recruitment (n=1859)

13C Urea Breath Test (79% positive)

Randomization (n=1463)

- Triple
- Sequential
- Concomitant

6-8 weeks: UBT + evaluation (n=1414)

- Hp positive
- Hp negative
- Hp unknown

Quadruple

1 year: UBT + evaluation (n=1340)
14-day triple, 5-day concomitant, and 10-day sequential therapies for *Helicobacter pylori* infection in seven Latin American sites: a randomised trial


- **Triple** (*n*=488) 82.2%
  - *p* = 0.002
- **Concomitant** (*n*=489) 73.6%
  - *p* = 0.04
- **Sequential** (*n*=486) 76.5%
  - *p* = 0.30

Greenberg ER, Lancet 2011
14-day triple, 5-day concomitant, and 10-day sequential therapies for *Helicobacter pylori* infection in seven Latin American sites: a randomised trial

Community-based recruitment (n=1859)

13C Urea Breath Test (79% positive)

Randomization (n=1463)

Triple
Sequential
Concomitant

6-8 weeks: UBT + evaluation (n=1414)

Hp positive
Hp negative
Hp unknown

Quadruple

1 year: UBT + evaluation (n=1340)
### One Year *H. pylori* Eradication Status

<table>
<thead>
<tr>
<th>Antibiotic Regimens</th>
<th>UBT Group % (95%CI)</th>
<th>n / N</th>
<th>Intention to Treat % (95%CI)</th>
<th>n / N</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>79.3% (77.1-81.5)</td>
<td>1063 / 1340</td>
<td>72.7% (70.4-74.9)</td>
<td>1063 / 1463</td>
<td>0.61</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.28</td>
</tr>
<tr>
<td>Triple, 14 days</td>
<td>80.4% (76.4-83.9)</td>
<td>364 / 453</td>
<td>74.6% (70.5-78.4)</td>
<td>364 / 488</td>
<td></td>
</tr>
<tr>
<td>Sequential, 10 days</td>
<td>79.8% (75.8-83.5)</td>
<td>356 / 446</td>
<td>73.3% (69.1-77.1)</td>
<td>356 / 486</td>
<td></td>
</tr>
<tr>
<td>Concomitant, 5 days</td>
<td>77.8% (73.6-81.6)</td>
<td>343 / 441</td>
<td>70.1% (65.9-74.2)</td>
<td>343 / 489</td>
<td></td>
</tr>
</tbody>
</table>
*H. pylori* eradication success at one year, by site

<table>
<thead>
<tr>
<th>Site</th>
<th>Success Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colombia</td>
<td>71.2</td>
</tr>
<tr>
<td>México, Obregón</td>
<td>72.8</td>
</tr>
<tr>
<td>México, Tápachula</td>
<td>75.8</td>
</tr>
<tr>
<td>Nicaragua</td>
<td>76.8</td>
</tr>
<tr>
<td>Chile</td>
<td>81</td>
</tr>
<tr>
<td>Honduras</td>
<td>87.3</td>
</tr>
<tr>
<td>Costa Rica</td>
<td>89.7</td>
</tr>
</tbody>
</table>

$p <0.001$
# One year eradication: by age and gender

<table>
<thead>
<tr>
<th>UBT Group</th>
<th>Number of subjects (N = 1340)</th>
<th>Eradication rate (%)</th>
<th>95% Confidence Interval (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males, age 45-70</td>
<td>202 / 236</td>
<td>85.6</td>
<td>80.5 - 89.9</td>
</tr>
<tr>
<td>Males, age 20-44</td>
<td>247 / 301</td>
<td>82.1</td>
<td>77.3 – 86.2</td>
</tr>
<tr>
<td>Females, age 45-70</td>
<td>265 / 320</td>
<td>82.8</td>
<td>78.2 – 86.9</td>
</tr>
<tr>
<td>Females, age 20-44</td>
<td>349 / 483</td>
<td>72.3</td>
<td>68.0 – 76.2</td>
</tr>
</tbody>
</table>
# One Year Eradication: Multivariate analysis

<table>
<thead>
<tr>
<th>UBT Group</th>
<th>Subjects (N = 1340)</th>
<th>Eradication rate % (95%CI)</th>
<th>Adjusted p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study site</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High(2), &gt;85%</td>
<td>360/407</td>
<td><strong>88.5</strong> (85.0-91.2)</td>
<td>0.002</td>
</tr>
<tr>
<td>Low(5), 71-81%</td>
<td>703/933</td>
<td>75.4 (72.5-78.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>449/537</td>
<td><strong>83.6</strong> (80.2-86.5)</td>
<td>0.009</td>
</tr>
<tr>
<td>Female</td>
<td>614/803</td>
<td>76.5 (73.4-79.3)</td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 50</td>
<td>323/384</td>
<td><strong>84.1</strong> (80.1-87.4)</td>
<td>0.001</td>
</tr>
<tr>
<td>40-49</td>
<td>278/344</td>
<td>80.8 (76.3-84.6)</td>
<td></td>
</tr>
<tr>
<td>20-39</td>
<td>462/612</td>
<td>75.5 (71.9-78.7)</td>
<td></td>
</tr>
<tr>
<td><strong>Adherence</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 80% pills</td>
<td>1017/1249</td>
<td><strong>81.4</strong> (79.2-83.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>&lt; 80% pills</td>
<td>34/75</td>
<td>45.3 (34.6-56.6)</td>
<td></td>
</tr>
<tr>
<td><strong>Household</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>653/801</td>
<td><strong>81.5</strong> (78.8-84.2)</td>
<td>ns</td>
</tr>
<tr>
<td>Crowding</td>
<td>404/534</td>
<td>75.8 (72.2–79.4)</td>
<td></td>
</tr>
</tbody>
</table>

*Adjusted for site, age, sex, crowding, adherence
## H. pylori Recurrence rate at One Year

<table>
<thead>
<tr>
<th>Antibiotic regimens</th>
<th>Total Subjects (n / N)</th>
<th>Recurrence Rate (%)</th>
<th>95% Confidence Interval (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>125 / 1091</td>
<td>11.5</td>
<td>9.9 – 13.3</td>
</tr>
<tr>
<td><strong>Antibiotic regimens p-value</strong></td>
<td></td>
<td></td>
<td>0.62</td>
</tr>
<tr>
<td>Triple, 14 days</td>
<td>47 / 389</td>
<td>12.1</td>
<td>8.8 – 15.3</td>
</tr>
<tr>
<td>Sequential, 10 days</td>
<td>36 / 356</td>
<td>10.1</td>
<td>7.0 – 13.2</td>
</tr>
<tr>
<td>Concomitant, 5 days</td>
<td>42 / 346</td>
<td>12.1</td>
<td>8.7 – 15.6</td>
</tr>
</tbody>
</table>
## Program Effectiveness at One Year: Cost per Cure

<table>
<thead>
<tr>
<th>Treatment Regimen</th>
<th>6-8 week Intervention (UBT retest &amp; retreat)</th>
<th>Single treatment analysis (No UBT retest &amp; retreat)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>UBT-negative (%)</td>
<td>Cost per UBT-negative(USD)</td>
</tr>
<tr>
<td>Triple</td>
<td>80.5%</td>
<td>$44</td>
</tr>
<tr>
<td>Sequential</td>
<td>79.8%</td>
<td>$39</td>
</tr>
<tr>
<td>Concomitant</td>
<td>77.8%</td>
<td>$39</td>
</tr>
</tbody>
</table>
## Program Effectiveness at One Year: Cost per Cure

<table>
<thead>
<tr>
<th>Treatment Regimen</th>
<th>6-8 week Intervention (UBT retest &amp; retreat)</th>
<th>Single treatment analysis (No UBT retest &amp; retreat)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>UBT-negative (%)</td>
<td>Cost per UBT-negative (USD)</td>
</tr>
<tr>
<td>Triple</td>
<td>80.5%</td>
<td>$44</td>
</tr>
<tr>
<td>Sequential</td>
<td>79.8%</td>
<td>$39</td>
</tr>
<tr>
<td>Concomitant</td>
<td>77.8%</td>
<td>$39</td>
</tr>
</tbody>
</table>
Perspective: Shangdong Intervention Trial

Shangdong Intervention Trial, 1995-2010, 15 year follow-up
Design: 3365 randomized subjects, placebo-controlled
Factorial design 2x2x2: Vitamins, garlic, *H. pylori*
Treatment: omeprazole 20mg + amoxicillin 1g (bid, 14days)
Results: Significant reduction in GC incidence by 39% (ITT)
Trend towards GC mortality reduction (OR=0.67, 0.35-1.3)

### Gastric Cancer Incidence

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Adjusted for baseline histology only</th>
<th>Fully adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td><em>H. pylori</em> treatment</td>
<td>0.61 (0.39 to 0.96)</td>
<td>.034</td>
</tr>
<tr>
<td>Garlic</td>
<td>0.83 (0.56 to 1.23)</td>
<td>.36</td>
</tr>
<tr>
<td>Vitamin</td>
<td>0.85 (0.57 to 1.26)</td>
<td>.41</td>
</tr>
</tbody>
</table>

Ma JL, JNCI 2012
Latin America Hp RCT: Take Home Points
Morgan DR, JAMA 2013

Treatment RCT results (patients)
Triple therapy for 14 days “esta vivo”
Regional studies are necessary to optimize therapies
  RCT results in USA & Europe may not be generalizable
Regional studies are needed:
  Countries, regions, patient populations
  Treatment efficacy, antibiotic resistance

1-year cohort results (populations)
Eradication programs to prevent GC may be warranted
Programs warrant specific design (site, gender, age)
Novel biomarkers & therapies are needed
Gastric Cancer Prevention Program

- Diet and Nutrition
- HP Eradication (age<40, <IM)
- Endoscopy Surveillance (age>40, >IM)
- Education Supplements
- Pilot Study
- Risk populations
- Antioxidants
- Intervention
- Screening Program
ASGE Guidelines for Gastric IM and Dysplasia
GIE 2006

• Lack of evidence to recommend routine intestinal metaplasia surveillance in the U.S.

• Focused surveillance may be considered:
  ➢ Family history of gastric cancer
  ➢ Ethnic background

• If surveillance is performed
  ➢ Topographic biopsy mapping of stomach
  ➢ Appropriate dysplasia management
GC Progression: Netherlands Cohort Study, 1991-2004
deVries AC, Gastro 2008
GC Progression: Netherlands Cohort Study, 1991-2004  
deVries AC, Gastro 2008

<table>
<thead>
<tr>
<th>Initial Histology</th>
<th>Annual GC progression</th>
<th>HR Univariate</th>
<th>HR Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrophic Gastritis</td>
<td>0.1%</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Intestinal Metaplasia</td>
<td>0.25%</td>
<td>2.1 (1.8–2.5)</td>
<td>1.7 (1.5–2.1)</td>
</tr>
<tr>
<td>Dysplasia, mild/moderate</td>
<td>0.6%</td>
<td>5.05 (4.2–6.1)</td>
<td>3.9 (3.2–4.8)</td>
</tr>
<tr>
<td>Dysplasia, severe</td>
<td>1.2% (6.0% / 5 years)</td>
<td>55.9 (45.0–69.5)</td>
<td>40.1 (32.2–50.1)</td>
</tr>
</tbody>
</table>

**Conclusions:** Patients with premalignant gastric lesions are at considerable risk of gastric cancer. As current surveillance of these patients is inconsistent with their cancer risk, the development of guidelines is indicated.
Spain Cohort Study, GC Progression (1988-94 to 2005-07)
Gonzalez C, Int J Cancer 2010

<table>
<thead>
<tr>
<th>Factor</th>
<th>Hazard ratio</th>
<th>95% Confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (vs. female)</td>
<td>5.51</td>
<td>1.85–16.4</td>
</tr>
<tr>
<td>Univariate</td>
<td>2.34</td>
<td>0.72–7.61</td>
</tr>
<tr>
<td>Multivariate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (older than 60 yr)</td>
<td>4.18</td>
<td>1.12–5.6</td>
</tr>
<tr>
<td>Univariate</td>
<td>1.47</td>
<td>0.37–5.86</td>
</tr>
<tr>
<td>Multivariate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incomplete or predominant incomplete intestinal metaplasia (present vs absent at baseline)</td>
<td>13.7</td>
<td>4.92–38.0</td>
</tr>
<tr>
<td>Univariate</td>
<td>11.3</td>
<td>3.80–33.9</td>
</tr>
<tr>
<td>Multivariate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family history of GC (yes vs. no)</td>
<td>6.92</td>
<td>1.93–24.8</td>
</tr>
<tr>
<td>Univariate</td>
<td>6.11</td>
<td>1.67–22.4</td>
</tr>
<tr>
<td>Multivariate</td>
<td>0.43</td>
<td>0.13–1.40</td>
</tr>
<tr>
<td>NSAID use (more than 5 yr, vs. no)</td>
<td>0.43</td>
<td>0.12–1.49</td>
</tr>
</tbody>
</table>
Gastric biopsy topographic mapping, Sydney system
Dixon MF, AJSP 1996
NBI for gastric precancerous lesions
Pimental-Nunes P, Endoscopy 2012
Management of Gastric Precancerous Lesions

• General screening / surveillance is not recommended in populations with a low risk of gastric cancer

• Gastric topographic mapping:
  - Minimum of 2-4 antral and 2-4 corpus biopsies

• Gastric topographic mapping is indicated for:
  - Index endoscopy in high risk patients
  - Surveillance endoscopy in patients with high risk precancerous lesions

• Higher risk groups include:
  - Family history of gastric cancer
  - Certain racial and ethnic groups
  - Immigrants from high incidence areas
Management of Gastric Precancerous Lesions

- Surveillance endoscopy may be warranted:
  - IM which is extensive or incomplete (q2-3 years)
  - The utility of the grading of IM severity is unclear
  - Low grade dysplasia (<12 months)
- High grade dysplasia warrants definitive treatment

- Hp eradication is indicated for patients with precancerous lesions of the stomach
- The role of pepsinogens awaits further study
  - Better biomarkers are needed
- Novel imaging technologies may be helpful
Gastric Intestinal Metaplasia Management Algorithm
Dinis-Ribeiro Endoscopy 2012; Correa AJG 2010

Pathology report with IM in a gastric mucosa biopsy sample

Assess for *H. pylori* infection (test with serology if biopsy is negative) and treat
Assess extension and type of IM in original biopsies

Extensive IM* or incomplete type

Repeat every 3 years if extensive IM/atrophy** or incomplete-type IM persists
Endoscopic surveillance with mapping or serum PG levels at 1 year

No surveillance required
Gastric cancer: Take Home Points

Leading cause of infection-associated cancer mortality
Globally, second leading cause of cancer mortality
In the U.S., a disease of minority populations

The Bermuda Triangle of risk directs prevention
Primary prevention is feasible through Hp eradication
New guidelines are in evolution for endoscopic surveillance of high risk populations
Novel imaging modalities will facilitate surveillance
EMR/ESD techniques will continue to evolve
Novel biomarkers are expected in the near term
¡Mil Gracias!