Screening and Surveillance for the Early Detection of Gastric Cancer

Society of Gastroenterology Nurses and Associates

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Case FG
- 63 year old African American male admitted for fatigue
- PMHx: HTN, GERD
- Meds: antiHTN, PPI
- FHx: noncontributory
- SocHx: grew up in Chicago, social EtOH, never tobacco
- ROS: (+) weight loss - ~20lbs/3-4 months
- Exam unremarkable
- Labs: Hb 7.4, microcytic

Endoscopy
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How could this happen...

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GASTRIC CANCER

Screening and surveillance for the early detection of GASTRIC CANCER

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Background

- Gastric cancer 4th most common cancer in the world
- 937,000 new cases per year, accounting for nearly 10% of all new cancers
- 2nd highest cause of cancer-related deaths worldwide → 700,000 deaths per year
- Wide global variation → 2/3 cases in developing countries
Mechanism

- Mechanism of gastric carcinogenesis complicated and largely unknown
- Majority is associated with histologically recognizable premalignant stages first described by Pelayo Correa in mid 1970's
- Chronic H. pylori infection is thought to initiate a premalignant cascade
- Sequence involves chronic superficial gastritis, atrophic gastritis, intestinal metaplasia, dysplasia, and invasive neoplasia

Burden of Disease

- High incidence
  - East Asia
  - Central America
  - South America

UNANSWERED QUESTIONS

- Benefits of surveillance have been evaluated and known
- How and who should be tested for H. pylori?
- What could be done before "dysplasia"?
  - at the point of "intestinal metaplasia"
- Who is considered higher than "average risk"?
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RISK FACTORS FOR GASTRIC CANCER

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Risk Factors

Habitat
• Smoking
• Nitrate high diet
• Low fresh fruit and vegetables
• Alcohol use

Host
• low socioeconomic class
• blood group A
• familial occurrence of gastric cancer
• H. pylori virulence
• Host genetics
• Interaction

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• Cigarette smoking
• HPV
• HCV
Screen for class 1 carcinogens
• H. Pylori
• The most successful human pathogen
• ~50% human population infected

We don't screen …

Busuttil RA and Boussioutas A. J Gastroenterol and Hepatology 2000;24:193-201

deVries AC and Kuipers EJ. Helicobacter 2007;12:22-31


1980s
• H. pylori discovered
1994
• NIH consensus conference recognized HP as a cause of gastric and duodenal ulcers
1994
• International Agency for Research on Cancer (IARC) and World Health Organization (WHO) classified H. pylori as a Class I (definite) human carcinogen

Your note?
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Complicated interrelationship

Majority of the course is benign

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<table>
<thead>
<tr>
<th>HP 60%</th>
<th>HP 40%</th>
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</thead>
<tbody>
<tr>
<td>AG 50%</td>
<td>AG 50%</td>
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<tr>
<td>AG 15%</td>
<td>AG 15%</td>
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<tr>
<td>IM 40%</td>
<td>IM 50%</td>
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<tr>
<td>IM 15%</td>
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</tbody>
</table>

The pattern to notice:
High prevalence of HP in all regions of the world

East vs. West


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2001: 12 case control studies within prospective cohorts

- H. Pylori positivity increases risk of developing gastric cancer 6 fold

2008: Prospective study over 9.4 years

- Patients infected with H. pylori have 10.9 fold higher chance of gastric cancer than uninfected

2007: Meta-analysis of long term impact of HP eradication on gastric cancer risk

- 8 studies, 10-137 months follow up

- IM may be a point of no return where progression to gastric cancer is inevitable

- Suggests HP eradication should precede onset of metaplastic lesions

Argument for screening for H. Pylori
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H. Pylori screening

- Gastric MALT lymphoma
- Active peptic ulcer disease
- Past history of documented peptic ulcer
- Test and treat for dyspepsia (<55yo and no alarm symptoms)


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H. Pylori screening

- Patients who are on ppi longterm
- Prior to treatment with NSAIDs
- Unexplained iron deficiency anemia
- Unexplained vitamin b12 deficiency
  * Asymptomatic not tested

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New recommendations

- Talley NJ et al.  Gastric cancer consensus conference recommends Helicobacter pylori screening and treatment in asymptomatic persons from high-risk populations to prevent gastric cancer.  AJG 2008;103:510
- Chey WD et al.  Practice Parameters Committee of the ACG.  ACG guideline on the management of Helicobacter pylori infection.  AJG 2007;102:1808

Asian pacific guidelines
- Population based screening for high risk groups

European guidelines
- Population based screening for high risk groups

ACG guidelines
- Describe high risk populations but consider strategies for screening such groups as controversial

WHO to screen

- *Population based screening for high-risk groups
- *Population based screening for high-risk groups
- Describe high-risk populations but consider strategies for screening such groups as controversial
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Case FG

- Urea breath test: negative
- Endoscopy:
- Pathology:
  - Mass: invasive adenocarcinoma
  - Random: atrophic gastritis and multiple foci of intestinal metaplasia involving the antrum and corpus of the stomach
  - H. pylori negative

No H. pylori?...

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Choosing the right test

- Clinical setting
- Pretest probability
- Sensitivity and specificity
- Cost effectiveness and availability

Gatta L. Am J Gastro 2004;99:823

HOW to screen

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Endoscopic testing

- Rapid Urease Test
  - Hydrolysis of urea
  - Sens 90-95%
  - Spec 95-100%
- Histology
  - Sens >95%
  - Spec >95%
  - Limited by cost, not usually needed
- Culture
  - Only for sensitivity in refractory disease

Non-invasive testing

<table>
<thead>
<tr>
<th>Breath urea</th>
<th>Stool Ag</th>
<th>Serology</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Hydrolysis of urea</td>
<td>• Detects HP via enzyme</td>
<td></td>
</tr>
<tr>
<td>• Sens 88-95%</td>
<td>• Sens 96%</td>
<td>• Sens 94%</td>
</tr>
<tr>
<td>• Spec 95-100%</td>
<td>• Spec 86-92%</td>
<td>• Spec 100%</td>
</tr>
</tbody>
</table>

False negatives

Recommended as test of choice
Most accurate noninvasive test for active HPI

False negatives
Decreased sensitivity

Mechanism of decreasing sensitivity
- Increase in gastric pH
- Rise in periplasmic pH in HP
- Decrease in internal urease activity
- Decrease bacterial density
- May be responsible for decreased sensitivity in both tests

Watch out for false negatives
Meds
Blood
Mucosa
Decreased sensitivity
Aim: to determine if sensitivity of Urea Breath Test (UBT) and H. pylori Stool Antigen Test (HpSA) is decreased with PPI

Prospective single blind randomized study

n=152 patients/6 mo with H. pylori infection

HP infection
– rapid urease (+) and histology
– or culture (+) alone

Gatta l. Am J Gastro 2004;99:823

Results

Baseline

After treatment

Sensitivity:

UBT

72.9 - 85.4%

Antacid

100%

PPI

90.0%

Stool Test

83.0%

Conclusion:
PPI decreases sensitivity of UBT and HpSA
Antacid will not alter sensitivity of UBT or HpSA
And Ranitidine or Bismuth?

Gatta L. Am J Gastro 2004;99:823
Bravo L et al. Am J Gastroenterol 1999; 94: 2380-83

14-52%
15-36%
PPI
44-55%
15-25%
Bis
5-18%
5%
H2B
UBT
HpSA
False negative rates

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Points to consider when using tests of active infection

How soon?
• As early as one day
When returns to positivity?
• Reliably after 2 weeks off PPI
• Ranitidine may have tolerance effect

Who's on a PPI?

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Who's on a PPI?

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Case FG

• Endoscopy:
  • Urea breath test: negative
  • Pathology:
    – Mass: invasive adenocarcinoma
    – Famine: atrophic gastritis and multiple foci of intestinal metaplasia involving the antrum and corpus of the stomach
    – Hp negative

Patient FG was on PPI!
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Watch out for false negatives

- Decreased sensitivity

Gatta 1. Am J Gastro 2004;99:823

Meds Blood Mucosa

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Acute GI bleeding

- Meta-analysis of 23 studies
- Mean prevalence 63-80%
- Multiple diagnostic modalities assessed
- Gold standard for diagnosis based on at least one independent diagnostic method

- 0.67 RUT
- 0.70 Histo
- 0.93 UBT
- 0.87 HpSA

High prevalence setting → raise index of suspicion

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Watch out for false negatives

- Decreased sensitivity

Gatta 1. Am J Gastro 2004;99:823

Meds Blood Mucosa

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Gastritis and chronic inflammation were severe when H. pylori existed in the gastric mucosa, as expected. In contrast, the degree of atrophic gastritis and IM was more severe in the seropositive only group compared to other two groups (seropositivity + histology positive, and seronegative). Suggest that the progression of atrophic gastritis and intestinal metaplasia seems to drive H. pylori out of the gastric mucosa.

H. pylori IgG positivity with negative invasive tests represents past infection rather than false negative.

Case FG
• Endoscopy:
• Urea breath test: – negative
• Pathology:  
– Mass: invasive adenocarcinoma
– Random: atrophic gastritis and multiple foci of intestinal metaplasia involving the antrum and corpus of the stomach
– H. pylori negative
No H. pylori?...
Did this confound results in patient FG?

Non-invasive testing
• Breath urea
  • Hydrolysis of urea
  • Sens 88-95%/spec 95-100%
  • False positives rare
• Stool Ag
  • Detects HP via enzyme immunoassay
  • Sens 94%/spec 86-92%
  • False positive in UGIB - cross-reactivity with blood
• Serology
  • Elisa to detect IgG
  • Sens 90-100%
  • Spec 76-96%
  • Prevalence affects ppv
  • If <20% → (+) HP active infection ~50% of the time

Useful:
• High pretest probability (ulcer), may treat based on positive serology
• Confirm negative serology
• Low pretest probability (young dyspepsia, low prevalence area), negative useful to exclude infection, confirm positive serology

Gatta l. Am J Gastro 2004;99:823
Case FG

- **Endoscopy:**
  - Negative

- **Urea breath test:**
  - Negative

- **H. Pylori Serology:**
  - Positive

**Pathology:**

- Mass: invasive adenocarcinoma
- Random: atrophic gastritis and multiple foci of intestinal metaplasia involving the antrum and corpus of the stomach.
- H. pylori negative

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**The downsides?**

- **Not active infection:**
  - 12-18 months to clear Ab.
  - Ask the patient!

- **Not cost effective:**
  - Economic model: 50yo Japanese Americans, screening with HP serology was more cost effective than mammography.

- **Abx complications:**
  - Most significant issues with 3rd gen cephalosporins, FQ, Abx resistance

- **Abx resistance:**
  - Not usually w. standard HP Rx Abx

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**H. pylori antibody is FOREVER**

- Titers decline by approximately 50% at 3 months
- 60% have undetectable titers at 18 months
- After therapy, seroconversion from detectable to undetectable levels have specificity of 100% for detecting the eradication

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**Useful in:**

- IgG
- IgA
- Faecal antigen

- Gastric biopsy
- Useful 1 to 3 post tx eradication
The prevalence of disease is low

The question: what is the prevalence among patients in Chicago?

- Caucasian: 32%
- Hispanic: 29%
- Asian: 5.5%
- American Indian: 0.5%
- African American: 33%
- Eastern Europe?

Poles and Serbians in Chicago are their largest ethnic communities outside of Poland and Serbia.

Prevalence of H. pylori

Malaty H et al.  Gastroenterology 1992;103:813-6

N=485, Houston
N=7465, Nhanes
N=108, Houston

Based on serology
- asymptomatic patients
- adjusted for age, income, education, other clinical factors

Sero-positivity significantly higher in African American and Hispanic population.
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Prevalence of H. pylori

- **Caucasian**
  - 24%
  - 15%

- **African American**
  - 28%
  - 29%

- **Hispanic**
  - 40%
  - 36%

Clinical symptoms were not associated with HP positivity (but ethnicity was)

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The prevalence is decreasing

- **2012 update**
  - Overall seroprevalence decreased from 33% to 11%

- **Caucasian**
  - 34%
  - 26%
  - 26%
  - 21%

- **African American**
  - 70%
  - 66%
  - 53%
  - 52%

- **Hispanic**
  - 65%
  - 62%
  - 63%

Decline in HP seroprevalence affects primarily the Caucasian population

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Grad Y et al. Am J Epidemiol 2012;175:54-9

Hispanic

African American

Caucasian

Overall

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Does treatment reduce risk of gastric cancer?

- Meta-analysis 2009 – 7 trials
  - Significantly lower rate of gastric cancer in patients randomized to eradication
  - 1.1 vs. 1.7% (RR 0.65, 95% CI 0.43-0.98)

High incidence areas (China, Japan, Columbia)

- Placebo controlled trial, n=3365; 14.7 yr f/u
  - Significant reduction in gastric cancer incidence in patients who underwent eradication
  - 3.0% vs. 4.6% (OR 0.61, 95% CI 0.38-0.96)

China, 15 year follow up

- Mass eradication study over 5 years
  - There was decrease in pudi and gastric cancer
  - Taiwan, 5 year follow up

Eradication seems to reduce the risk of gastric cancer in "high risk" patients.

Benefits of surveillance has been evaluated and known

- H. pylori should be treated if found
- If low grade dysplasia is detected, surveillance EGD with topographic mapping

For US, the progression of IM to cancer is low and surveillance is not indicated for the average risk patient

ASGE guideline: the role of endoscopy in the surveillance of premalignant conditions of the upper GI tract.

GIE 2006;63: 570-580

UNANSWERED QUESTIONS

- Who is considered higher than "average risk"?
- What could be done before "dysplasia?"
  - at the point of "intestinal metaplasia"
- How and who should be tested for H. pylori?

Gastric Intestinal Metaplasia?

- Adaptive response to environmental stimuli such as HP infection, smoking, high salt intake
- Gastric mucosa is replaced by mucosa that resembles intestinal epithelium
- Morphologically characterized by mucus secreting goblet cells
- Typically asymptomatic
- May be associated with achlorhydria, P IBS, bloating, flatulence, abdominal discomfort, and diarrhea
- High association of IM with gastric cancer

Leung WK et al. Aliment Pharmacol Ther 2002;16:1209-1216
Busuttil RA and Boussioutas A. J Gastroenterol and Hepatology 2000;24:193-201
Slovenia:
- Patients with IM have a >10-fold increased risk of developing gastric cancer.

Japan:
- IM conferred a 6.4x higher risk of developing gastric cancer.

China:
- OR for gastric cancer ranged from 17.1 to 29.3.

Increased risk of gastric cancer are from varying populations (not just Asia).

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RATIONALE FOR/AGAINST SURVEILLANCE?

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Against surveillance

- Developed countries: low prevalence, low yield, high cost
- Gastric IM is difficult to recognize endoscopically (unlike premalignant lesions of esophagus and colon)
- Findings at conventional endoscopy often still correlate poorly with histology diagnoses
- Differences in training and approach from Western vs. Asian countries (especially Japan), where lesions are frequently established on endoscopy vs. histologic evaluation of random biopsies
Endoscopic findings may be subtle.

Which is intestinal metaplasia?
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Pro screening/ surveillance

• Many compelling reasons

Leung WK et al.  Aliment Pharmacol Ther 2002;16:1209-1216

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• Aim: investigate whether the eradication of HP reduces risk of developing gastric cancer
• Nippon Fukuyama Hospital outpatient clinic, 1995-2003
• n=1342 consecutive patients with PUD and who had received HP eradication

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Methods


Index endoscopy
n=1342
evaluate ulcers, background gastric mucosa, HP infection

495 du, 776 gu, 1995-99: 619 pts, 2 wk dual therapy (amox 750 bid/ ppi bid)
1997-03: 670 pts, 1 wk triple tx (amox 750 bid/clarith 200mg or 400mg bid)
1995-03: 53 pts, 1 wk metronidazole 500 bid, amox 750 bid, or clarithro 200mg bid and ppi bid

Confirm eradication
• 1-2 months after tx
• Breath test and f/u endoscopy performed to determine HP status

n=1120 completed >/= 1 year
• endoscopy and urea breath tests yearly
• followed for up 8.6 years (mean 3.4y)

HP cured when bacterial culture, urease test, and urea breath test all negative
71 both
Methods


Index endoscopy

n=1342
evaluate ulcers, background... infection

n=1120
completed \(\geq 1\) year

cured of infection

n=176
persistent infection

n=8
Gastric cancer

n=4
Gastric cancer

All gastric cancer in patients with GU, none in DU (\(p=0.005\))

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- Aim:
  1. Identify risk factors for progression of gastric IM
  2. Identify high-risk subgroup that might warrant intensive surveillance

- University of China Hong Kong
- Volunteers residing in Yantai county of Shandong invited for screening endoscopy
- Randomized control study over 5 years.
- HP+ patients received either anti-HP therapy or placebo


Compelling reason #2:
- Eradication is not enough

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- n=587 HP (+)
- n=220
- n=215
- n=292
- n=295
- 1 week tx
- 152
- LTFU
- f/u endoscopy
- 5 year analysis
- n=164 (74.5%)
- n=20 (9.3%)
- n=6 cancers
- 10 (2.3%) developed invasive gastric ca during f/u
- n=4 cancers
- HP clearance confirmed by histology


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Results

- Eradication of HP infection significantly retards but does not eliminate IM progression
- 52.9% had progression of IM over 5 years

Conclusions:
- Identified a subgroup (age + persistent HP) at high risk of progression that may warrant more intensive endoscopic surveillance
Example of Japan
Compelling reason # 3 – EVIDENCE OF UTILITY
Lee, KJ et al. Int J Cancer 2006:118;2315-2321
1986: Case control study in farm village, Osaka
• OR of death from stomach cancer in screened vs. unscreened was 0.519 males / OR 0.486 females
• Effective in reducing stomach cancer mortality by half
1988: Prospective cohort study, 12 year follow up in Japan
• Incidence rate same
• RR diagnosing advanced stomach cancer 0.4-0.7
• Effective in reducing mortality from stomach cancer
Prospective study over 13 year f/u in Japan involving 42,150 patients
• 2 fold decrease in mortality in screened vs. unscreened patients (RR=0.52;95% CI 0.36-0.74)
• Significant decrease in incidence of advanced gastric cancer in screened subjects 
(RR = 0.75;95% CI=0.58-0.96)

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Aim: to determine the incidence of gastric cancers in this “high risk” (IM, ulcers, polyps) group and to evaluate the potential for early diagnosis and treatment

Dyspepsia clinics in area of the Queen Elizabeth and Sandwell District General Hospital, 1984-1988
• Patients over age 45 referred to dyspepsia clinic

Compelling reason # 4 – EVIDENCE OF UTILITY 
EXTENDS BEYOND ASIA

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Methods
n=14 cancers (8.4%)
n=166 accepted
n=368 (21%) lesions requiring f/u
n=22 (1.3%) gastric cancer
n=1753 OAE
• offered surveillance endoscopy

Requiring followup:
• dysplasia, IM, AG, foveolar hyperplasia, regenerative changes, polyps, ulcers
• annual endoscopy
• ulcers re-examined q2mo until healing

• 10 years follow-up
Results

- More cancers detected from surveillance were of an earlier stage than those detected at open access.
- 5-year survival was significantly higher than tumors detected at open access.

Stage distribution between surveillance and open access

<table>
<thead>
<tr>
<th>Stage</th>
<th>Surveillance</th>
<th>Open Access</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>15%</td>
<td>23%</td>
</tr>
<tr>
<td>II</td>
<td>30%</td>
<td>10%</td>
</tr>
<tr>
<td>III</td>
<td>25%</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>30%</td>
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</tbody>
</table>

In patients with IM, annual surveillance may delay trend toward an earlier stage with major improvement in survival.

Conclude:

- In patients with IM, annual surveillance can detect most new tumors at early stage with major improvement in survival.

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Compelling reason #5

- Perspective on the burden of disease
- Esophageal vs. gastric cancer
  - Incidence of disease after detection of premalignant lesions

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BE is a strong risk factor for esophageal adenocarcinoma

- Annual risk = 0.12% (lower than assumed 0.5%)
- Risk is increased to 0.26% when high-grade dysplasia included

HP(+) is a strong risk factor for gastric adenocarcinoma

- Annual risk = 0.37%
- Risk is 0.5%/year HP(+)
- 0.24%/yr HP eradication
UNANSWERED QUESTIONS

- Benefits of surveillance has been evaluated and known
- How and who should be tested for H. pylori?
- “What could be done before dysplasia?”
- At the point of “intestinal metaplasia”
- Who is considered higher than “average risk”?

ASGE Guidelines

Who is considered higher than “average risk”?
What could be done before “dysplasia”?
At the point of “intestinal metaplasia”
How and who should be tested for H. pylori?

UNANSWERED QUESTIONS

Proposed Strategy for Screening and Surveillance for low prevalence regions

Epidemiologic Risk Factors
Serologic Screening
Histologic Evaluation
Endoscopic Surveillance

Identify population for noninvasive screening
Identify premalignant lesions at risk of progression
HP eradication
Early tx dysplasia

Management Algorithm

Characterize:
- histologic subtype (complete vs incomplete)
- extent (limited vs. extensive)
- determine the risk of malignancy and guide surveillance

No surveillance
Individualize:
surveillance EGD
Repeat EGD mapping in 3 yrs
High risk patient?
Surveillance EGD mapping q2-3 yrs

High risk patient:
- Family history gastric ca
- Noncaucasian: African American, Hispanic, Asian
- Immigrant: East Asia or mountainous Latin America

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The discrepancy...

IM is a premalignant state
We do not offer surveillance
We do not individualize risk factors
The United States is a diverse place
H. pylori is a carcinogen
We do not screen for it

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How do we change?
Identify
Test
Treat
Eradicate

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How do we change?

Family history
H. pylori infection
Refractory gastric ulcers
Refractory gastric cancer
Abnormal gastric histology:
- Intestinal metaplasia
- Atrophic gastritis
- Autoimmune gastritis
- Hyperplastic/hyperplastic polyps
- Hyperplasia/hyperplastic polyps
- Carcinoids
- Regenerative changes
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How do we change?

- Known
- Benefit
- Unknown
- Low prevalence places
- Unknown
- High risk populations amongst low prevalence places

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Take Home Points

- Patients at risk for developing gastric cancer can be identified by ethnicity, country of origin, HP status
- HP screening and eradication may reduce the risk of gastric cancer
- Surveillance of high risk lesions may increase detection of early stage gastric cancer and therefore reduce mortality
- Given inherent diversity of the US, there may not be a true "average" risk patient; risk assessment needs to be individualized
- There is a role for targeted screening and surveillance for gastric cancer amongst "high risk populations" within a traditionally "low risk region"

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THANK YOU!

Questions?