Gastric Cancer, Gastritis and the Role of H. pylori

Prof. Anthony Axon

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World Organisation of Digestive Endoscopy

• Honorary Professor of Gastroenterology University of Leeds UK
• Past President BSG, ESGE, UEGF, OMEDE

Gastric cancer mortality is second only to lung cancer

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Aims of this presentation

• Understand the natural history of Hp gastritis
• Review the evidence showing Hp to be an essential risk factor for gastric cancer
• Discuss the mechanisms involved in gastric carcinogenesis
• Appreciate why gastric cancer incidence varies
Acute infection with *H. pylori*

- Usually occurs in childhood
- 7-10 day incubation
- Epigastric pain, flatulence and halitosis
- Anorexia with mucous vomiting
- Achlorhydria
- Symptoms resolve but the infection often persists
- Transmission unknown

Acute gastric inflammation immediately after infection with *Helicobacter pylori*

[Image: Sobala et al., Gut (1991) 32(11) 1415-1418]

Chronic gastritis with “activity” in the antrum some years following infection

[Image: Normal, healthy antrum | Infected antrum]
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**Helicobacter gastritis before and one month after treatment**

Before treatment

After treatment

Dixon, Current Diagnostic Pathology (1994) 1, 80-89

**H. pylori gastric mucosa interactions**


**Development of atrophy and intestinal metaplasia after many years of infection**
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H. pylori, gastric atrophy and IM
a multicentre study of 2455 patients

Natural history of Hp Gastritis
• Acute infection (days)
• Chronic inflammation (years)
• Atrophy and intestinal metaplasia (severity and time)
• Hypochlorhydria (loss of parietal cells)
• Overgrowth of oral and intestinal bacteria
• Hp disappears and serology reverts

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Meta analysis of nested studies showing association between Hp and gastric cancer


Gastric cancer and infection with H. pylori using IgG ELISA serology

- Odds ratio of 3 is not enough to draw the conclusion that Hp is a necessary factor
- All the nested studies used standard anti-Hp ELISA serology
- The studies may have underestimated the odds ratio

Odds ratio 2.2 (95% confidence interval 1.4-3.6)
Ekstrom et al., Gastroenterology (2001) 121: 784-791

Gastric cancer and infection with H. pylori (corrected for CagA serology)

Odds ratio 21.0 (95% confidence interval 8.3-53.4)
Ekstrom et al., Gastroenterology (2001) 121: 784-791
Helicobacter gastritis and gastric acidity

High acid

Low acid

Type of gastritis and cancer risk, an 8 year prospective study of 1526 patients

<table>
<thead>
<tr>
<th>Gastritis</th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrophy</td>
<td></td>
</tr>
<tr>
<td>None or mild</td>
<td>1.0</td>
</tr>
<tr>
<td>Moderate</td>
<td>1.7 (0.8-3.7)</td>
</tr>
<tr>
<td>Severe</td>
<td>4.9 (2.8 - 19.2)</td>
</tr>
<tr>
<td>Distribution</td>
<td></td>
</tr>
<tr>
<td>Antral predominant</td>
<td>1.0</td>
</tr>
<tr>
<td>Pan gastritis</td>
<td>15.6 (6.5 - 36.8)</td>
</tr>
<tr>
<td>Corpus predominant</td>
<td>34.5 (7.1-166.7)</td>
</tr>
<tr>
<td>Intestinal metaplasia</td>
<td></td>
</tr>
<tr>
<td>Absent</td>
<td>1.0</td>
</tr>
<tr>
<td>Present</td>
<td>6.4 (2.6-16.1)</td>
</tr>
</tbody>
</table>


Corpus atrophy in gastric cancer, findings in 105 cancers

Nearly all cancer patients have corpus atrophy

Komoto et al., Am J Gastroenterol (1998) 93: 1271-6
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Gastritis
- Mild gastritis (No complications)
- Duodenal ulcer
- Severe antral gastritis
- Gastric ulcer
- Severe corpus or pan gastritis
- Atrophy IM
- Low Acid
- High Acid
- Cancer

The Mongolian gerbil

H. pylori and gastric cancer
- Nearly all cancer cases have been infected with Hp
- Gastric cancer is associated with corpus predominant atrophy and IM
- These changes are caused by long standing Hp infection
- Corpus gastritis is the main predictor for gastric cancer
- Animal models show that Hp infection leads to cancer

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- Appreciate why gastric cancer incidence varies

Does Hp itself directly cause gastric cancer?
- Antral predominant gastritis does not cause cancer
- Duodenal ulcer doesn’t become neoplastic
- H. pylori does not infect intestinal metaplasia
- 25% of gastric cancer cases develop after H. pylori has disappeared
- Gastric cancer is common in pernicious anaemia

Physiological effects of chronic gastritis, atrophy and intestinal metaplasia

The Correa hypothesis
- Hypochlorhydria
- Overgrowth of metabolically active intestinal organisms
- Increase of mutagenic reactive oxygen species in the mucosa
- Absence of luminal ascorbic acid
- Increased cell turnover
- This leads to cancer
Epithelial cell proliferation before and after *Hp* eradication

<table>
<thead>
<tr>
<th>Condition</th>
<th>Before</th>
<th>Immediately after treatment</th>
<th>One year later</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (n=21)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Hp</em>+ve (n=42)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Hp</em>+ve (n=42)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Failure (n=11)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Success (n=36)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Failure (n=6)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Lynch et al., Gut (1995) 38: 345-350

Intragastric ascorbic acid concentration before and after *Hp* eradication

<table>
<thead>
<tr>
<th>Condition</th>
<th>Before</th>
<th>After</th>
</tr>
</thead>
<tbody>
<tr>
<td>B=Before treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A=After treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal (n=53)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reactive gastritis (n=34)</td>
<td>1210</td>
<td>70</td>
</tr>
<tr>
<td><em>Hp</em> gastritis (n=77)</td>
<td>23885</td>
<td>112</td>
</tr>
</tbody>
</table>

Sobala et al., Gut (1993) 34, 1038-41

Reactive oxygen species in *H. pylori* gastritis

<table>
<thead>
<tr>
<th>Histology</th>
<th>Chemiluminescence (cpm/mg)</th>
<th>Malondialdehyde (nmol/litre)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (n=53)</td>
<td>1210</td>
<td>70</td>
</tr>
<tr>
<td>Reactive gastritis (n=34)</td>
<td>1576</td>
<td>89</td>
</tr>
<tr>
<td><em>Hp</em> gastritis (n=77)</td>
<td>23885</td>
<td>112</td>
</tr>
</tbody>
</table>

Drake et al., Gut (1998) 42: 768-771
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Effect of treatment

<table>
<thead>
<tr>
<th></th>
<th>Success</th>
<th>Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before (S)</td>
<td>After (S)</td>
</tr>
<tr>
<td>Chemiluminescence</td>
<td>16103</td>
<td>1141***</td>
</tr>
<tr>
<td>Malondialdehyde</td>
<td>122</td>
<td>99**</td>
</tr>
</tbody>
</table>

p<0.001***
p<0.01**

Drake et al., Gut (1998) 42: 768-771

Stem cells

- Ordinary tissue cells have a limited life span
- Stem cells are long lived and essential for the structural maintenance of the organ
- Embryonic stem cells differentiate into peripheral stem cells
- Peripheral stem cells are tissue specific
- The bone marrow can provide an emergency team to help in acute injury
- These are the Bone Marrow Derived Cells (BMDCs)

Bone marrow derived cells (BMDCs)

- These provide cells for short term repair
- They include stem cells
- Bone marrow stem cells are versatile
- They can take over the role of gastric stem cells
- As in chronic inflammation with atrophy
- They are unstable and produce metaplastic offspring
- These may become dysplastic
Bone marrow derived cells and gastric cancer

Control

Sham infected

4/52

20/52

>12/12


New model for the development of gastric cancer


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World map of gastric cancer mortality
Estimated age-standardised mortality rate per 100,000; Stomach: male, all ages

Why does gastric cancer vary in incidence?

- Prevalence of H pylori
- Severity of gastritis
- Pattern of gastritis

Helicobacter pylori infects those who are socio-economically disadvantaged

- The poverty in the UK during the 19th-20th century
Japanese versus British gastritis

- Japan – very high incidence, UK – relatively low

Comparison of gastritis in matched populations from Japan and England

- 252 age matched consecutive patients in Tokyo and Leeds/Bradford
- Gastritis assessed histologically
  - Severity
  - Pattern

Intestinal metaplasia and atrophy in matched populations from Japan and England

Naylor, Gotoda et al. (2004)

Naylor et al., Gut (2006) SB: 1545-1552
Differing patterns of gastritis in Japan and England


Dietary factors in the development of gastric cancer

- Fruit and vegetables are negatively associated
- Low dietary vitamin C is positively associated
- Vitamins not protective in prospective studies
- Nitrogenous products may be positively associated
- Salt is strongly associated and also increases risk in animal studies

Riboli and Norat, pub health nutr (2001) 4: 475-484
Effects of the CagA pathogenicity island

- Are the H. pylori organisms in Japan more virulent than those in the UK?
- CagA positive organisms, which are more virulent, are present in greater numbers in the far east
- But CagA is only one virulence factor, there are many other factors

High virulence H. pylori genotypes increase the risk of non-cardia cancer

221 chronic gastritis
222 gastric cancer

<table>
<thead>
<tr>
<th></th>
<th>Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>VacAs1</td>
<td>17</td>
</tr>
<tr>
<td>VacAm1</td>
<td>6.7</td>
</tr>
<tr>
<td>CagA+ve</td>
<td>15</td>
</tr>
</tbody>
</table>


Genetics and gastric cancer

- Interleukin-1 (IL-1) is an inflammatory cytokine
- IL-1β inhibits gastric acid secretion x 100 PPI
- The IL-1 gene cluster on 2q is polymorphic
- IL-1B-31T+ and IL-1RN*2/*2 have an odds ratio of 7.5 and 2.1 for gastric cancer

Proinflammatory cytokine gene polymorphisms increase the risk of non-cardia gastric cancer

<table>
<thead>
<tr>
<th>Polymorphism</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-1β-511</td>
<td>2.3</td>
</tr>
<tr>
<td>IL-1RN</td>
<td>3.6</td>
</tr>
<tr>
<td>TNF-α-308</td>
<td>2.2</td>
</tr>
<tr>
<td>IL-10</td>
<td>2.5</td>
</tr>
<tr>
<td>One polymorphism</td>
<td>2.8</td>
</tr>
<tr>
<td>Two polymorphisms</td>
<td>5.4</td>
</tr>
<tr>
<td>Three or more</td>
<td>27.3</td>
</tr>
</tbody>
</table>


Proinflammatory cytokine polymorphisms enhance the carcinogenic effect of high virulence *H. pylori* genotypes

<table>
<thead>
<tr>
<th><em>H. pylori</em></th>
<th>Host</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-1RN</td>
<td>3.3</td>
<td></td>
</tr>
<tr>
<td>IL-1β-511</td>
<td>3.3</td>
<td></td>
</tr>
<tr>
<td>VacAs1</td>
<td>87</td>
<td></td>
</tr>
<tr>
<td>VacAm1</td>
<td>7.4</td>
<td></td>
</tr>
<tr>
<td>VacAs1</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>VacAm1</td>
<td>8.8</td>
<td></td>
</tr>
<tr>
<td>CagA</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>CagA</td>
<td>7</td>
<td></td>
</tr>
</tbody>
</table>


Helicobacter gastritis and gastric acidity

High acid  Low acid
Inflammation in the corpus increases when acid secretion is reduced

- Corpus inflammation increased after 4 weeks omeprazole
  - Solcia, Scand J Gastro 1994
- Significant increase in severity after 4 weeks ranitidine
  - Meining, APT 1997
- Worsened significantly after 1 year PPI Rx
  - Stolte, APT 1998

Development of corpus atrophy in infected patients treated with acid suppression

- Atrophy increased at a rate of 6.1% per year
- Atrophy developed at a rate of 2.7% per year
  - Lundell Gastroenterology 1999
- Atrophy occurred at a rate of 4.7% per year
  - Klinkenberg-Knol Gastroenterology 2000
- Annual incidence of atrophy 2.5%
  - Lamberts Digestion 2001

Increasing acid secretion in Japan
Acid secretion is related to lean body mass

Baron JH, Gut (1985) 36: 637-642

Increasing height of men in Europe 1960-1990


Immune experience

- Immune experience may influence the type of inflammatory response to H. pylori
- Animals infected with Helminths develop a Th2 response to Hp infection
- These animals have a reduced degree of gastric atrophy
- This if extrapolated to humans might explain some of the differences in disease prevalence

Fox et al., Nature medicine (2000) 6: 536-542

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Summary

- *Helicobacter pylori* is a necessary factor in the causation of most non-cardia gastric cancer
- It may not be the direct cause of cancer
- Severe corpus gastritis is the phenotype that predicts cancer
- This is affected by environmental factors; diet, age and immune experience
- *H. pylori* and Host genetics and acid secretion