Helicobacter pylori
Commensal or Pathogen?

Vietnam 2004

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It was very difficult for gastroenterologists and physicians to accept the proposal of these two investigators, Marshall and Warren, who stated in 1983 that spiral bacteria in the human stomach were likely to be the cause of ulcers and stomach cancer.

Established gastroenterologists and scientists found it hard to accept the teachings of the two Australians! Instead, most gastroenterologists of the time assumed that Helicobacter were commensals which merely colonized people with ulcers or gastritis.
First Attempt at Publication: 1983

Dear Dr. Marshall,

I regret that your research paper was not accepted for presentation...

The number of abstracts we receive continues to increase and for this meeting 67 were submitted and we could only accept 56.

Score = bottom 20%

As shown here, our discovery was not “appreciated” by Australian gastroenterologists (read text from slide). Our discovery was rated in the lowest 20% and was not accepted even for a poster!

I only show this slide to remind young investigators that they should always keep their rejection letters. Although it is too painful to read them now, you may be proved correct in the future and then you can proudly display them.
Because of this rejection, in 1984 it was necessary for me to drink a culture of Helicobacter pylori to prove to the skeptics that Hp could cause gastritis and was not just a commensal present in people with ulcers or stomach cancer. This was published in the Medical Journal of Australia and in an editorial for The Lancet. Many gastroenterologists took notice but were determined to prove me wrong! However, it stimulated much of the successful research which we have seen presented since that time.
The self infection in 1984 fulfilled Koch’s postulates for H.pylori, proving that it caused gastritis. This shows a silver stain of the gastric mucosa with the acute infection. The black helical organisms are seen on damaged (brown) epithelial cells. Note that the cells do not have the normal transparent mucus content usually seen in the gastric epithelial layer.
This high power view reminds us that the gastric wall has a mucus layer to keep the acid from touching the mucosa and digesting it.

This diagram shows how the mucus barrier works. Here you see the mucus above in green and the cells below. In the lumen of the stomach is the acid represented by the H+. The surface of the mucus layer can actually repel water and acid. This enables the cells below to remain healthy because even though the stomach acid is strong, with pH of 2.0, the pH down on the cells (below the mucus barrier) is about 6.0.

In addition, a greasy component of the mucus gel (hydrophobic phospholipid) tends to repel water and acid from it.

H. Pylori damages this barrier in two ways. Directly by its phospholipase and proteases which make the mucus layer less repellant to water and acid. Indirectly by causing mucus cells to separate, become loosened from each other, stimulating the inflammatory response causing cells from below the mucosa to migrate through the epithelium.
Epidemiology and Disease Associations of *H. pylori*

Many studies have shown variants on the association with peptic ulcer, gastric cancer, and gastric lymphoma. In any developed country, about 20-30% of the population are infected with Helicobacter pylori (*H. pylori*). It is within this group that peptic ulcer disease develops. The great majority of duodenal ulcers and gastric ulcers are in the infected patients shown as the red inner circle.

Although the majority of persons with *H. pylori* are asymptomatic at any point in time, many of them eventually develop disease. In prospective studies, the conversion rate to active peptic ulcer is about 1% per annum. Thus, during a lifetime, about one third of infected persons develop symptomatic disease. In addition, persons with *H. pylori* have a 1%-5% chance of developing gastric cancer in their lifetime.

In Vietnam, with a population of 80 million people, there are probably 40 million with *Hp*.

The fact that so many people with *Hp* never actually develop disease has been reason for continuing controversy about Helicobacter.

Perhaps *Hp* is not always so bad. Actually there are several factors which affect the ultimate outcome of *Hp* infection, some in the organism, some in the host, and some in the environment.
In many cases of H. pylori infection, the mucosa appears normal or only slightly irregular.

The association between H. pylori and peptic ulcer is well known, but in many persons the endoscopy is normal. Peptic ulcer disease is a condition characterised by remissions and relapses so that the ulcer crater is not always present at endoscopy. One visible lesion found to be the best predictor of gastritis is the cobblestone, “gooseflesh” or “chicken skin” appearance of the antral mucosa. Other appearances such as redness remain for many years after treatment of the gastritis so they cannot be used as indicators of active Helicobacter infection.
Gastritis is always present in persons with *H. pylori*.
Before discussing variations in the pathogenicity of Hp, I wish to emphasize that Gastritis is always present in persons with Hp.
Here is the histology characteristic of Hp showing infiltration of the gastric mucosa with chronic inflammation – lymphocytes macrophages and plasma cells. These cells are making IgG antibody which allows serological detection to work quite well. Also there is acute inflammation present with scattered neutrophils.
Even though some Hp are worse than others, ALL PERSONS with Hp HAVE SOME DEGREE OF CHRONIC GASTRITIS AND THIS BECOMES MORE SEVERE AND EXTENSIVE IN THE STOMACH WITH TIME.
Cancer Incidence and Mortality

The countries are listed sorted both by cancer mortality and by cancer incidence. Note that in Japan, incidence is far greater than mortality. This is because effective screening programs detect gastric cancer at an early stage and cure is possible.

Although high gastric cancer usually correlates with *H. pylori* prevalence, there are some notable exceptions. UAR and Kuwait are known to have a 50-70% prevalence of *H. pylori*, but have rather low cancer mortality. Kenya is the representative African country with a rather low gastric cancer rate but a high *H. pylori* prevalence. This paradox, referred to as the “African enigma” by some, demonstrates that cancer causation from *H. pylori* must be modulated by many factors. These could be dietary, ethnic and bacterial strain related.
All Hp cause gastritis
- Gastritis is worse if CagA pathogenicity island is present
- CagA has various pathogenic potentials
  - East Asian (Japan - severe)
  - Asian (Vietnam - mixed)
  - Western (mild)

But the pathogenicity of Hp varies according to the presence and type of CagA toxin.
### Distribution of the Diversity of the CagA Protein in Japan

<table>
<thead>
<tr>
<th>Condition</th>
<th>n</th>
<th>East Asian</th>
<th>Western</th>
<th>cagA (-)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic gastritis</td>
<td>87</td>
<td>70</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td>Gastric cancer</td>
<td>54</td>
<td>53</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Note that in patients with gastric cancer in Japan, almost all will have the East Asian type of CagA. (Azuma T, Ohtani M, Yamazaki Y, Higashi H, Hatakeyama M. Meta-analysis of the relationship between CagA seropositivity and gastric cancer. Gastroenterology 2004;126(7):1926-7.)
Type of CagA and the Risk of Cancer

Azuma and co-workers suggest that cancer rates are related to the CagA type predominating in each country.

This table is preliminary data and has not been confirmed yet. It was just a letter to a journal. The number of strains tested from many countries is quite low.

However, the bad news is that strains from Vietnam appear to be very similar to Japanese strains – East Asian Type in the majority. This means that they have quite a strong cancer potential.

Contrast this with Thailand where Western style CagA strains are more common and cancer incidence is lower.

**Hp is unique – almost a commensal**

This cartoon emphasizes the location of Helicobacter beneath the gastric mucus layer, attached to the stomach mucus cells. The bacteria actually avoid the very acidic stomach contents (at top) where the pH is 2.0, instead, they stay at the bottom of the mucus layer. But Helicobacter do not survive where oxygen levels are high such as in the tissues. Therefore they remain half way between the oxygenated tissue and the low oxygen environment of the stomach contents. This means that Helicobacter can never become invasive like other pathogens. This location creates problems for the immune system which cannot eradicate gastric bacteria. If the immune response is too aggressive, the mucosal barrier will break and ulceration will occur. There is some evidence that Hp can down-regulate the immune system, thus allowing it to persist.
Virulence Factors of H. pylori

In-vitro studies using cultured epithelial cells have identified many factors secreted by H. pylori which cause pathologic changes. Most of these factors are present in the majority of Hp strains, but they may vary in their pathogenicity.

Urease is essential for colonization because it protects from acid allowing the bacterium to survive long enough to reach the mucosa.

Nap increases inflammation by attracting neutrophils.

BabA, is an adhesin responsible for attaching Hp to the epithelial cells. If the adhesion is strong, then the other toxins have far more effect.

Lewis antigens affect the ability of Hp to down-regulate the immune response perhaps by mimicking carbohydrates in the mucosa.

VacA and CagA, I will discuss in detail below. CagA toxin is part of the “Cag pathogenicity island” also referred to as the “CagPAI”.

PicB is a component of the CagPAI which is an ATPase responsible for driving the CagPAI machinery. It causes release of IL-8 and attracts neutrophils.
Secretion Systems

CagA is a toxin associated with the Cag pathogenicity Island (CagPAI). Bacteria have numerous secretion systems. Type IV secretion refers to the ability of some bacteria to create a “molecular syringe”, which is a modified flagellum or pilus structure, through which bacterial proteins and even genes can be injected into a host cell.

The prototype of this mechanism is the Type IV system of Agrobacterium which is extensively used to create new GM varieties of plants such as Vitamin enriched rice etc.
Type IV Secretion Homologues

Genes present in Hp and various other Type IV systems
VacA Toxin:
VacA toxin is present in all Helicobacters. But when the CagA pathogenicity island is present, then a more virulent form of VacA is present. VacA is secreted from the Hp bacterium where, in the presence of low pH, it polymerizes to form a membrane channel. It inserts into the epithelial cell membrane and creates a pore through which anions can pass. The cell becomes leaky, perhaps to the advantage of the attached Hp organism. The channels also insert into intracellular organelles causing vacuoles to form.
The Molecular epidemiology of Hp

The Molecular epidemiology of Hp can be studied as shown here. The principle relies on the fact that there is redundancy in the genetic code. This slide shows the genetic codes which can form each amino acid. Notice that changes in the third base of a codon often does not change the amino acid. So, taking the case of Glycine, mutations affecting the third base, which can be U, C, A or G, all code for Glycine. Thus mutations here do not affect the Hp bacterium and go unnoticed in evolution. However, they can be counted to measure the number of years since strains have diverged from one another.
**Human and Helicobacter Migrations**

If Hp was merely a pathogen, we might find that it was only recently acquired by humans. However, if Hp was a commensal, then we might expect that Hp has evolved with man for millions of years, as has the rest of the intestinal flora.

By studying the sequence variations of CagA, VacA and various other essential “housekeeping” genes (present in all Hp strains), several groups have mapped the global migration of Hp in parallel to the known human migrations.

This world map indicates the direction of human migrations (arrows) and time range (years since migrations happened), as taken from Cavalli-Sforza (47) and Diamond (48). The geographic centers of the major Hp genotypes known today are indicated by concentric circles of different colors. It appears that Hp followed man during the migrations indicated by the arrows, giving rise to the present genotype distribution (indicated by circles).

Light green areas indicate the locations where the development of agriculture and animal breeding was initially started, resulting in the expansion of the initial human populations (46-48).

So far, it appears that Hp has followed humans for at least 50,000 years. Thus, perhaps Hp resembles a commensal in some ways.
Natural History of *Helicobacter pylori* Infection.

*H. pylori* is usually acquired in childhood. Acute *H. pylori* infection causes transient hypochlorhydria and is rarely diagnosed.

Chronic gastritis will develop in virtually all persistently colonized persons, but 80 to 90 percent will never have symptoms.

The further clinical course is highly variable and depends on bacterial and host factors. Patients with higher acid output are likely to have antral predominant gastritis, which predisposes them to duodenal ulcers. Patients with lower acid output are more likely to have gastritis in the body of the stomach, which predisposes them to gastric ulcer and can initiate a sequence of events that, in rare cases, leads to gastric carcinoma.

*H. pylori* infection induces the formation of mucosa-associated lymphoid tissue (MALT) in the gastric mucosa.

Malignant lymphoma arising from such acquired MALT is another rare complication of *H. pylori* infection.
Helicobacter pylori infection and the development of gastric cancer.

By itself, H.pylori rarely causes cancer. Cancer only occurs in long term infection where acid secretion is suppressed or removed by atrophic gastritis.

Here is an important paradox about H.pylori and Cancer
Perhaps there is some reason for a little optimism about Hp. Helicobacter is said to be a risk factor for stomach cancer. But this important observation has been largely overlooked. Stomach cancer rates for persons with a history of duodenal ulcer are normal, or even lower than normal.

In this prospective study reported in the New England Journal of Medicine, Uemura performed surveillance endoscopy on patients with Hp for up to 12 years. He observed that about 4% developed stomach cancer during that time.

But there was no stomach cancer in patients who had duodenal ulcer, even though duodenal ulcer is associated with the more harmful, toxin producing, strains of Helicobacter.

Thus, by itself, Helicobacter does not always cause cancer. Cancer probably only occurs in long term infection where acid secretion is suppressed or removed by atrophic gastritis.

When stomach acid is normal or high, as it is in duodenal ulcer patients and most persons with Helicobacter, cancer risk is actually low. This observation has also been made in seroepidemiologic studies in California (Parsonnet NEJM) and Hawaii (Nomura NEJM).
The upper graph shows that even in a Western country, older persons have a high prevalence of *H. pylori* because they acquired the infection in childhood.

The lower graph illustrates a developing country where the infection rate is 20% per annum and the loss of the infection rate is 3% per annum. Vietnam is in transition so we expect to see the pattern change over the next generation.

Things which will decrease the new Hp cases are smaller families and improved public health measures, particularly drinking water quality.
### Demographics

As you know even more than I do, Vietnam has a young population so most people do not yet experience a cancer risk from Hp. As shown here, in 2004, only 5.6% of the population is above the age of 65 years. The average age is 25 years.
Gastric cancer and Age – Data from Japan

More than 2800 new cases of stomach cancer occur in persons under the age of 44 year but most (10,000 or so) are in persons above the age of 60. As the population ages, and lifespan increases, gastric cancer will become more and more important. That is why Hp needs attention now.
End
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