

***Helicobacter Pylori* and Peptic Ulcer Disease: A Paradox.**

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H*elicobacter pylori* infection is an unsolved paradox. *H. pylori* infection paradox is while this bacteria is found almost exclusively in humans and infects around 80% of the human population in developing countries like India but causes gastro-duodenal diseases in only 15% of the infected individuals in their lifetime.¹ *H. pylori* is the leading cause of peptic ulcer disease by causing antral predominant inflammation while it causes gastric cancer by causing gastric mucosal atrophy. Same bacteria but different diseases caused by different pathogenetic mechanisms with different outcomes and prognosis. However, disease outcomes are related to the pattern and severity of chronic inflammation in the gastric mucosa, which in turn is influenced by both bacterial and host factors¹.

Peptic ulcers are breaks in the lining of the duodenal or gastric mucosa, most commonly caused by *H. pylori* and nonsteroidal anti-inflammatory drugs. Peptic ulcer disease is associated with significant mortality and complications include hemorrhage and perforation. *H. pylori* eradication heals existing ulcers and prevents their recurrence².

H. pylori is the causative agent in over 75% of duodenal ulcer cases. Antral-predominant inflammation leads to increased gastric acid output. Gastric metaplasia of the duodenal epithelium then permits *H. pylori* to colonize and cause inflammation, which may lead to duodenal ulceration. *H. pylori* is also the leading cause of gastric ulcers, which develop in patients with pancreatitis. Here the acid output is normal or reduced, thus preventing the development of duodenal ulcers, but gastric ulcers may develop. Premalignant lesions and gastric adenocarcinoma may also arise^{3,4}.

H. pylori produces numerous virulence factors, many of which are highly polymorphic, phase variable, genetically linked, and/or have diverse and sometimes opposing functions. The cagPAI is a 40 kb horizontally transmitted segment of DNA. It encodes a T4SS, with CagL at the tip of the needle-like structure which binds to $\alpha 5\beta 1$ integrin on host cells⁵. CagA, an immunodominant 120-145 kDa protein, is injected into cells through the T4SS together with peptidoglycan peptides. This process activates NF- κ B, triggering the secretion of pro-inflammatory cytokines and chemokines.

Virtually all *H. pylori* strains possess the vacA gene but it is highly polymorphic, with two alternative allelic variants for the signal (s1/s2), intermediate (i1/i2), and mid- (m1/m2) regions. The mid-region plays a role in host cell binding, and m1 forms are able to bind a wider range of cell types than m2. s2 and i2 VacA have reduced activity compared to the s1 and i1 variants^{6,7}.

The tfs4 gene cluster comprises dupA and other vir homologues which are thought to encode a type IV secretion system⁸. Although dupA was initially identified as a duodenal ulcer-promoting virulence factor, numerous subsequent conflicting studies have left the role of dupA in disease unclear. This is likely due to the requirement for other components of the tfs4 to produce a functional type IV secretion system, making dupA alone an imperfect marker⁹. The presence of dupA in clinical *H. pylori* isolates is associated with increased IL-8 levels in the antrum of infected individuals¹⁰.

In the article "Prevalence of *Helicobacter pylori* infection in patients with perforated duodenal ulcer: a hospital based study" published in this edition of JIMSA¹¹ is important in several respects. The study looks at the prevalence of *h.pylori* among 75 patients of perforated duodenal ulcer over one year duration. More than half of the biopsies had evidence of *h.pylori* which shows that *h.pylori* is the pre-dominant cause of peptic ulcer disease related perforation. Interestingly one of the patients had a diagnosis of adenocarcinoma.

Despite over 2 decades of intensive research, there remains an incomplete understanding of the circumstances leading to disease development, due to the fascinating complexity of the host-pathogen interactions. There is accumulating data concerning the virulence factors associated with increased risk of disease, and the majority of these have pro-inflammatory activities. Despite this, only a small proportion of those infected with virulent strains develop disease.

Thus, we need more such studies to solve the paradox of *H.pylori*.

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