Peptic ulcer disease: current notions

Helicobacter pylori infection and non-steroidal anti-inflammatory drugs (NSAIDs) are the two most important aetiological factors in peptic ulcer disease (PUD). While host genetic factors and dietary factors might also play a role, to date there is insufficient data to implicate these in the aetiology of PUD. A range of H. pylori virulence factors, including the cytotoxin associated gene A and the vacuolating cytotoxin A, have been linked with both increased levels of inflammation and PUD. A further virulence factor known as the duodenal-ulcer promoting gene A has been specifically associated with an increased risk of PUD worldwide. Although increasing reports of H. pylori negative PUD has led some to question the role of H. pylori in PUD, investigations of this issue suggest that H. pylori negative PUDs are mainly due to NSAIDs usage and to false negative results related to diagnostic methods.

Prior to the discovery of Helicobacter pylori, peptic ulcer disease (PUD), which encompasses both gastric (GU) and duodenal (DU) ulcers, was believed to be due to gastric acid, the common dictum being ‘No acid, no ulcer’. The discovery and initial isolation of H. pylori by Robin Warren and Barry Marshall, and their subsequent fulfilment of Koch’s postulates showing a pivotal role for H. pylori in gastritis, the underlying pathology associated with PUD and gastric cancer, not only revolutionised our understanding of gastroduodenal disease but lead to antibiotic therapies that could cure PUD. The global impact and importance of their discovery was recognised in 2005 when Marshall and Warren received the Nobel Prize in Physiology or Medicine.

Currently, extensive scientific evidence shows that the two major aetiopathological factors involved in PUD are infection with H. pylori and ingestion of non-steroidal anti-inflammatory drugs (NSAIDs)2,5. Although gastric acid hyper-secretion is still considered to be a necessary factor, it is not a sufficient aetiological factor.

Each year PUD affects 4 million people worldwide with complications reported in 10–20% of these patients, and ulcer perforation in 2–14% of cases6. The annual incidence of PUD ranges 0.10–0.19% and 0.03–0.17% for physician-diagnosed and in-hospital-diagnosed PUD, respectively7. Over recent decades, the incidence of PUD has decreased significantly, which is believed to be due to the decrease in H. pylori infection, particularly in developed countries5. Currently, GU is more commonly associated with use of NSAIDs, especially in older patients and those with comorbidities, in whom widespread prescription of NSAIDS and suboptimal adherence to gastroprotective therapy is common6.

Pathogenesis of peptic ulcer disease

Helicobacter pylori and peptic ulcer disease

In all those infected with H. pylori the outcome of colonisation is a chronic active gastritis. However, the gastric distribution of H. pylori and the severity of the chronic inflammatory response might differ according to the colonising strain, host genetics and immune response, diet, and the level of acid production. While the majority of those infected develop no other complications and are often free of any obvious clinical symptoms, approximately 10% of those infected will develop PUD7.

An important predisposing factor related to PUD is an individual’s level of gastric acid secretion, as this determines the location of gastritis7. In subjects with reduced levels of gastric acid, a pangastroitis results, which predisposes to GU, whereas in subjects in whom gastric acid secretion is increased, an antral-predominant gastritis develops, which predisposes to DU7.
**H. pylori** infection impairs negative feedback of acid secretion by impairing somatostatin release and its subsequent inhibitory control of gastrin release from G cells, leading to functional disruption of antral-fundic neural connections. The immunopathogenic aspect of ulcerogenesis is primarily driven by the influx of neutrophils and macrophages into the gastric mucosa in response to **H. pylori** colonisation, with the release of lysosomal enzymes, leukotrienes and reactive oxygen species that impair mucosal defence.

**H. pylori** virulence factors, including adaptive enzymes, toxins and mediators of inflammation, lead to bacterial persistence in the stomach and disruption of the gastric mucosal barrier. Production of alkaline ammonia by **H. pylori** urease prevents D cells in the antral glands from sensing the true level of acidity, leading to inappropriate release of somatostatin. It has been suggested that **H. pylori** strains from ulcer patients produce higher amounts of this enzyme than do those from people without ulcers.

A wide range of **H. pylori** virulence factors have been associated with more serious disease outcome. Of these, the cag pathogenicity island (cagPAI), the vacuolating cytotoxin A (VacA) and the duodenal ulcer promoting gene A (dupA) have received the most scrutiny in relation to PUD.

The **H. pylori** cagPAI is a 40 kb DNA insertion element that encodes up to 32 genes including the cytotoxin gene A (caga) and genes encoding a type IV secretion system (T4SS). The T4SS has been shown to translocate the CagA protein into host gastric epithelial cells where it is tyrosine phosphorylated at the Glu-Pro-Ile-Tyr-Ala (EPIYA) motifs by the cellular kinases Src and Ab1. Four classes of EPIYA motifs, designated EPIYA-A to -D, as determined by the 32 amino-acid sequence of the core Glu-Pro-Ile-Tyr-Ala motif have been identified. The EPIYA-C (predominantly found in Western strains) and -D motifs (predominantly found in Eastern strains) are the major sites of tyrosine phosphorylation within CagA and are not only necessary for further interaction between CagA and SHP-2, but determine the strength of this interaction, the extent of SHP-2 deregulation, and the extent of hummingbird phenotype induction in vitro.

Further, translocated CagA activates nuclear factor κB resulting in expression of interleukin (IL)-8 that leads to increased inflammation. In both Western and Eastern populations, caga positive strains of **H. pylori** have been associated with an increased risk of PUD. While **H. pylori** strains carrying CagA with multiple EPIYA-C motifs or an EPIYA-D motif have been linked with gastric cancer (GC) development, the majority of studies have failed to show an association with PUD. However, a recent study reported a significant association between an increased number of EPIYA-C motifs and GU.

The vacA gene is present in all **H. pylori** strains. While the majority of strains produce a VacA protein, only approximately 40% make the most active form of the toxin. The production and activity of VacA has been shown to relate to the presence of polymorphisms in three main regions of the vacA gene, the signal (s1 and s2), mid (m1 and m2) and intermediate (i1 and i2) regions. While vacA s1/i1/m1 strains are fully active, s2/i2/m2 strains are inactive. Recent association studies have shown that subjects infected with **H. pylori vacA** s1/i1/m1 strains develop more severe corpus inflammation and more severe antral and corpus neutrophil activity, and that **H. pylori vacA** s1/i1/m1 and s1/i1/m2 forms are associated with an increased risk of PUD and GC.

In 2005, the first disease-specific **H. pylori** virulence factor was identified and named dupA by Lu et al., who showed dupA to increase the risk of DU (odds ratio (OR): 3.1, 95% confidence intervals (CI): 1.7–5.7) but protect against gastric atrophy, intestinal metaplasia and GC. Although the association between dupA and DU has been supported by a number of subsequent reports, many studies have failed to show an association between dupA and DU. However, two recent global meta-analyses by Hussein et al. and Shiota et al., which included 2358 and 2466 individuals, respectively, concluded that worldwide dupA-positive subjects had indeed an increased risk of DU (OR: 1.4, 95% CI: 1.1–1.7 and OR: 1.41, 95% CI: 1.12–1.76, respectively). However, in both studies distinct geographical variations in the prevalence of the dupA gene, and the association between dupA and DU, were observed. Given this, a recent study by Jung et al. investigated if genetic differences in the makeup of the dupA gene may explain this disparity. In this study, the presence of a complete dupA cluster rather than dupA alone was found to be associated with the development of DU and increased IL-8 production, suggesting that the complete dupA cluster is required for full expression of this virulence factor.

**Nonsteroidal anti-inflammatory drugs and peptic ulcer disease**

NSAIDs have been shown to inhibit the synthesis of protective prostanooids in the gastric and duodenal mucosa, leaving the mucosa susceptible for subsequent ulceration by gastric acid. While animal studies have shown that neutrophil adherence to gastric microcirculation plays a critical role in initiation of NSAID damage, NSAID-related gastropathy in humans is characterised by an absence of inflammatory cells unless there is a concomitant **H. pylori** infection. However, it is not known if neutrophils can initiate NSAID damage in humans.
NSAIDs have also been shown to increase the risk of PUD complications. For example, the use of low-dose acetylsalicylic acid (ASA) increases the risk of ulcer bleeding by 2–3-fold compared with non-users\(^3^5\). This has been mainly attributed to ASA antiplatelet action on a pre-existing \(H. pylori\)-related ulcer, rather than its ulcerogenic effect as an NSAID\(^3^5\).

### Other factors and peptic ulcer disease

It has been suggested that mucosal resistance to the effect of acid might be a key factor in PUD pathogenesis. For example, the presence or absence of protective substances in staple diets including certain phospholipids, sterols, and sterol ester fractions in lipids, which protect the gastric mucosa, has been related to geographical differences in the prevalence of duodenal ulceration\(^5^6\). These substances have been shown to exert protective activities against both gastric and duodenal ulceration, including NSAIDs-associated ulceration, and also promote healing of ulceration\(^5^6\).

Although smoking is not a primary cause of PUD, it has been reported to regulate aggressive and protective factors in the gastric mucosa, and therefore, it might be still considered an important contributor to the pathogenesis of PUD\(^5^7\).

Studies examining the possible role of host genetic factors in ulcerogenesis have reported genetic polymorphisms in the nucleotide-binding oligomerisation domain-containing protein (NOD1), the metabolizing enzyme cytochrome P450 2C19 (CYP2C19) and IL-8 to be associated with an increased risk of PUD\(^5^8\–\(^5^9\). In contrast, specific polymorphisms in IL-1\(\beta\), toll like receptor (TLR) 4 and TLR1 have been negatively correlated with the disease\(^4^0\–\(^4^2\).

### Conclusions

\(H. pylori\) infection and NSAIDs are the two most important aetiological factors in PUD. In addition to the \(H. pylori\) virulence factors \(cagA\) and \(vacA\), a novel biomarker known as \(dupA\) increases the risk of DU worldwide. Further investigations assessing the role of factors such as diet and host genetic polymorphisms in PUD pathogenesis need to be conducted. \(H. pylori\) eradication results in long-term cure of \(H. pylori\)-related PUD, thus, it is recommended in patients with PUD who are naive NSAIDs users.

### References

Under the Microscope


**Biographies**

**Dr Natalia Castaño-Rodriguez** (MD, MPhil) has worked in the fields of molecular biology, microbiology, biostatistics and bioinformatics related to genetics of cancer and immunogenetics. For the past 4 years, she has been working extensively on *Helicobacter pylori*-related gastric cancer, initially as a postgraduate student completing a MPhil program, and currently as a PhD candidate in Biochemistry and Molecular Genetics at The University of New South Wales.

**Professor Hazel Mitchell** is Head of Medical Microbiology in the School of Biotechnology and Biomolecular Science (BABS) at The University of New South Wales, Sydney, where she plays a major role in convening and teaching Medical Microbiology to Science and Medical students. For more than 25 years her research has focused on the gastric pathogen *Helicobacter pylori* including studies investigating the epidemiology, pathogenesis and the role of bacterial and host genetic factors in gastric cancer. In 1996 she was a founding organiser of the Western Pacific *Helicobacter pylori* study group and was convenor of the first meeting in Guangzhou, China and international scientific adviser for subsequent meetings in Malaysia, Indonesia, Australia, Japan and Thailand. In 2010 she co-edited the book ‘*Helicobacter pylori* in the 21st Century’ with Associate Professor Phil Sutton.

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