

# Mechanisms involved in *Helicobacter pylori* induced duodenal ulcer disease: an overview

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**Subject headings** *Helicobacter pylori*; *Helicobacter* infection; gastric acid; gastric mucosa; duodenal ulcer; bicarbonates; gastric metaplasia

Olbe L, Fändriks L, Hamlet A, Svennerholm AM, Thoreson AC. Mechanisms involved in *Helicobacter pylori* induced duodenal ulcer disease: an overview. *World J Gastroentero*, 2000;6(5):619-623

Duodenal ulcer (DU) can be developed via several different mechanisms. Hypersecretion of gastric acid is, however, a common denominator. A massive hypersecretion of acid can by itself evoke a DU, e.g. in the Zollinger-Ellison syndrome. Irrespective of the mechanism behind the development of a DU, powerful antisecretory treatment will heal the ulcer and prevent recurrence.

The hypersecretion of acid in DU patients is well characterized (Table 1). The maximal acid secretory capacity is increased in about half of the patients<sup>[1]</sup>, probably due to an enhanced trophic effect of gastrin on the oxyntic mucosa. Several mechanisms normally inhibiting gastric acid secretion, has been found defective in DU patients<sup>[2-4]</sup>, i.e. resulting in an increased release of gastrin<sup>[2]</sup>. The final result is a raised and prolonged acid response to every meal<sup>[5]</sup>.

The most common cause of DU is *Helicobacter pylori* (*H. pylori*) infection. It is, however, only a minority (10% - 15%) of all *H. pylori* infected subjects, who will develop DU. The sequence of events leading to DU includes hypersecretion of acid, development of gastric metaplasia in the proximal duodenum with colonization of *H. pylori* in the duodenal bulb, progress towards a high density of virulent *H. pylori* bacteria in the bulb with a marked active and chronic inflammation, and a profoundly reduced bicarbonate secretion in the bulb. The overview is a short presentation of evidence supporting this concept.

**Table 1** Gastric acid secretory characteristics of duodenal patients (all of which might be *Helicobacter pylori* induced)

Increased maximal acid secretory capacity
Increased parietal cell mass (trophic effect of gastrin?)
Increased basal acid secretion
Increased basal release of gastrin
Increased and prolonged acid response to meals
Increased release of gastrin
Defective inhibitory mechanisms
Antral acidification
Antral distension
Fat in the duodenum ( <i>H. pylori</i> induced?)

## *H. PYLORI* EFFECTS ON ACID SECRETION

A pronounced *H. pylori* induced inflammation of the antral mucosa in the presence of an intact oxyntic mucosa will result in acid hypersecretion, due to a blockade of mechanisms normally inhibiting gastric acid secretion<sup>[6,7]</sup>. It should be emphasized that this acid hypersecretion does exist in all subjects with a *H. pylori* infection predominantly localized to the antrum, and is thus not a characteristic only for DU patients.

If, however, a pronounced *H. pylori* induced inflammation also includes the oxyntic mucosa, the acid secretion will instead be reduced due to inhibition induced by *H. pylori* inflammation on parietal cell level and a subsequent development of atrophic gastritis<sup>[8]</sup>.

## Maximal acid secretory capacity

DU patients have a higher maximal acid secretory capacity than subjects without the ulcer disease, but there is a considerable overlapping between the two groups. *H. pylori* infection of the antrum results in a moderate increase of the release of gastrin from the antrum. Gastrin has a trophic effect on the acid secreting mucosa, that can produce a markedly increased maximal acid secretory capacity, e.g. in patients with the Zollinger-Ellison syndrome. Also moderately increased serum gastrin levels seem to be able to enhance the maximal acid secretory capacity<sup>[9,10]</sup>. For instance, eradication of *H. pylori* has been followed by a reduced maximal acid secretory capacity<sup>[9]</sup>. This conclusion is supported by the finding that resection of the antrum with retention of the whole acid secreting part of the

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**Received** 2000-07-05 **Accepted** 2000-08-01

stomach in DU patients markedly reduced the maximal acid secretory capacity<sup>[11]</sup>.

The substantial overlapping of the maximal acid secretory capacity between DU patients and subjects without ulcer can be explained partly by the fact that many subjects without ulcer have *H. pylori* infection and consequently an increased release of gastrin, and partly by the possibility that the balance between the gastrins having acid stimulatory effect and those having only trophic effect<sup>[12]</sup>, might vary from subject to subject.

### Defective inhibitory mechanisms

In subjects with a predominantly antral *H. pylori* infection the gastrin release is increased in the fasting condition, during meals, and by experimental administration of gastrin releasing peptide (GRP)<sup>[6,13-17]</sup>, which probably is a consequence of a reduction of the somatostatin in the antrum by the *H. pylori* infection<sup>[18,19]</sup>. Antral somatostatin acts as a physiological inhibitor of the gastrin release. After eradication of *H. pylori* the gastrin release is normalized. During i.v. infusion of GRP the gastrin release and acid secretion was significantly higher in *H. pylori* infected subjects, and these responses were normalized after eradication of *H. pylori*<sup>[20]</sup>. Interestingly the acid response to GRP in *H. pylori* infected DU patients was twice that in *H. pylori* infected subjects without ulcer despite similar gastrin responses in both groups. Whether this experimental situation reflects physiological conditions is open to question for several reasons, but the results indicate that DU patients may have a more pronounced hypersecretion of acid than *H. pylori* infected subjects without ulcer.

Antral *H. pylori* infection gives rise also to a blockade of an inhibitory nervous reflex from the antrum to the acid secreting mucosa<sup>[7]</sup>. In subjects without *H. pylori* infection distension of the antrum provokes an inhibition of acid secretion via a reflex pathway, and this inhibition is completely absent in subjects with *H. pylori* infection. The blockade of the inhibitory reflex is probably a result of the inflammatory process in the *H. pylori* infected antrum, since the inhibitory reflex seems to turn up again only when the inflammatory reaction has ceased after eradication of *H. pylori*.

The defective inhibitory mechanisms caused by antral *H. pylori* infection results in acid hypersecretion under physiological conditions. The gastrin release during meals is increased in *H. pylori* infected subjects<sup>[6,13-15]</sup>, and contributes to an increased and prolonged acid response to meals<sup>[15]</sup>. The well-known inhibition of gastrin release by acidification of the antrum is markedly impaired in *H. pylori* infected subjects<sup>[14,15]</sup>, contributing to the acid hypersecretion of the

infected subjects. The hypersecretion of acid obviously results in an increased acid load on the duodenal bulb<sup>[15]</sup> both in *H. pylori* infected subjects without ulcer and DU patients. Thus, it seems reasonable that the explanation for the fact that only a minority of all *H. pylori* infected subjects will develop DU has to be searched for in the duodenal bulb, but with acid hypersecretion as necessary prerequisite.

### GASTRIC METAPLASIA

Gastric metaplasia (GM) is islands of gastric mucosa in the duodenal bulb. GM develops as a result of an increased acid load on the bulb, and is e.g. rather extensive in patients with the Zollinger-Ellison syndrome<sup>[21]</sup>. GM has been found in 90% of *H. pylori* infected DU patients, and in about 60% of *H. pylori* infected subjects without ulcer<sup>[22,23]</sup>, in accordance with the increased duodenal acid load in both these groups. GM is a prerequisite for colonization of *H. pylori* in the duodenal bulb. It is possible that the extension of GM is facilitated by the *H. pylori* induced inflammatory process in the bulb, since a combination of *H. pylori* eradication and antisecretory treatment reduced the GM area more effectively than either treatment alone<sup>[25,26]</sup>.

Hypersecretion of acid and development of GM exists in both DU patients and *H. pylori* infected subjects without ulcer, albeit somewhat more pronounced in DU patients. It therefore seems reasonable to assume that a critical factor in the development of DU could be a large number of *H. pylori* and/or particularly virulent *H. pylori* in the duodenal bulb of DU patients. The density and virulence of *H. pylori* in DU patients has previously been determined in several studies, but in biopsies taken from the antrum. In these studies of antral *H. pylori* density and virulence, only a marginal difference was found between DU patients and *H. pylori* infected subjects without ulcer. However, findings regarding *H. pylori* in the antrum does not necessarily reflect the situation in the duodenal bulb.

GM in the duodenal bulb is found in patches that cannot be visualized at ordinary gastroduodenoscopy. In a recent study<sup>[24]</sup> the extent of GM in the duodenal bulb was therefore determined more systematically by taking 2 biopsies from each quadrant of the bulb. The area of GM in the multiple biopsies was 4 times larger in the DU patients than in the *H. pylori* infected subjects without ulcer<sup>[24]</sup>. These biopsies were also used to determine the prevalence and density of virulent *H. pylori* as well as the type (active and chronic) and degree of the inflammatory reaction in both the antrum and the duodenal bulb of DU patients ( $n = 20$ ) and *H. pylori* infected subjects without ulcer ( $n = 21$ ).

## BACTERIAL DENSITY AND *cagA* STATUS IN THE DUODENAL BULB

*H. pylori* colonization of GM in the duodenal bulb is very common. It was found in 95% of DU patients and in 80% of infected subjects without ulcer<sup>[24]</sup>, determined by quantitative culture<sup>[27]</sup>. Rigorous precautions were taken at the endoscopy to avoid contamination of the duodenal biopsies with *H. pylori* from the stomach. Gastric epithelial cells express the blood group antigen Lewis-b, and *H. pylori* have the ability to bind to these antigens, thereby facilitating the colonization of the mucosa<sup>[28]</sup>. *H. pylori* also has the ability to express various Lewis antigens, that might imply greater opportunity to escape the immune response of the host. It was recently shown<sup>[29]</sup> that *H. pylori* expressing various Lewis antigens exist in a considerably higher frequency in the duodenal bulb of DU patients (90%) than in the bulb of infected subjects without ulcer (42%).

The density of *H. pylori* was much lower in the duodenal bulb than in the antrum, even after correction for the area of GM<sup>[24]</sup>, suggesting that the environment in the duodenal bulb is less favourable for colonization of *H. pylori*. The mean *H. pylori* density in the bulb was about 20 times higher in DU patients than in infected subjects without ulcer, despite the fact that the bacterial density in the antrum was similar for both groups<sup>[24]</sup>. There was, however, a substantial overlap of the bacterial density in the bulb between DU patients and infected subjects without ulcer.

The clinically relevant virulence factors of *H. pylori* have not yet been identified. The presence of the *cagA* gene (cytotoxin associated gene A) is so far the best marker of virulence. *H. pylori* bacteria that are *cagA* positive can induce a more powerful release of proinflammatory cytokines with a subsequent potential of mucosal damage<sup>[30]</sup>. The proportion of *cagA* positive bacteria might therefore be a significant factor determining the local mucosal damaging effect of colonized *H. pylori*. DU patients had a much higher prevalence of *cagA* positive bacteria in the duodenal bulb (81%) than *H. pylori* infected subjects without ulcer (30%), despite the fact that the prevalence of *cagA* positive bacteria in the antrum was of the same order for both groups (86% and 75%, respectively)<sup>[24]</sup>. Furthermore, subjects with a predominance of *cagA* positive bacteria in the bulb had about 10 times higher bacterial density than subjects with *cagA* negative bacteria<sup>[24]</sup>.

## *H. PYLORI* INDUCED INFLAMMATION IN THE DUODENAL BULB

The *H. pylori* bacteria are colonizing the GM in the duodenal bulb, and consequently the inflammatory cells are found in connection with the GM. The

chronic duodenitis, determined by the degree of infiltration of lymphocytes, was found more marked in DU patients than in *H. pylori* infected subjects without ulcer, but again with overlapping between the two groups<sup>[24]</sup>. Active duodenitis, defined by the presence of neutrophil leucocytes, is an established and common finding in DU patients. Active duodenitis was found only in DU patients and almost exclusively in DU patients with *cagA* positive *H. pylori* in the bulb<sup>[24]</sup>. Active duodenitis is thus a characteristic for DU patients. Activation of neutrophil leucocytes can result in tissue damage by release of proteolytic enzymes<sup>[31]</sup> and by induction of reactive oxygen metabolites in the gastric epithelial cells<sup>[32]</sup>.

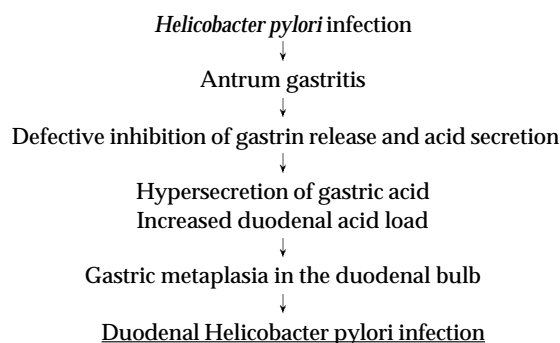
## BICARBONATE SECRETION IN THE DUODENAL BULB

Hypersecretion of gastric acid with increased duodenal acid load can result in mucosal damage and development of ulcer. Under normal circumstances the acidification of the duodenal bulb will immediately activate bicarbonate secretion from the duodenal mucosa resulting in neutralization of the acid with the formation of carbon dioxide and water. The carbon dioxide will then stimulate the nitric oxide (NO) producing enzyme NO-synthase<sup>[33]</sup>, that has been demonstrated in the duodenal mucosa<sup>[34]</sup>. NO will finally activate the bicarbonate secretion<sup>[35]</sup>.

DU patients have a markedly reduced bicarbonate secretion in response to acidification of the duodenal bulb<sup>[36]</sup>. It has been shown more recently that the bicarbonate secretion is normalized after eradication of *H. pylori*<sup>[37]</sup>, implying that the reduced bicarbonate response to acidification of the bulb is a result of the *H. pylori* infection. Interestingly, the bicarbonate secretion was found normal in *H. pylori* infected subjects without ulcer<sup>[37]</sup>. The *H. pylori* dependent reduction of the bicarbonate secretion is thus another characteristic of DU patients.

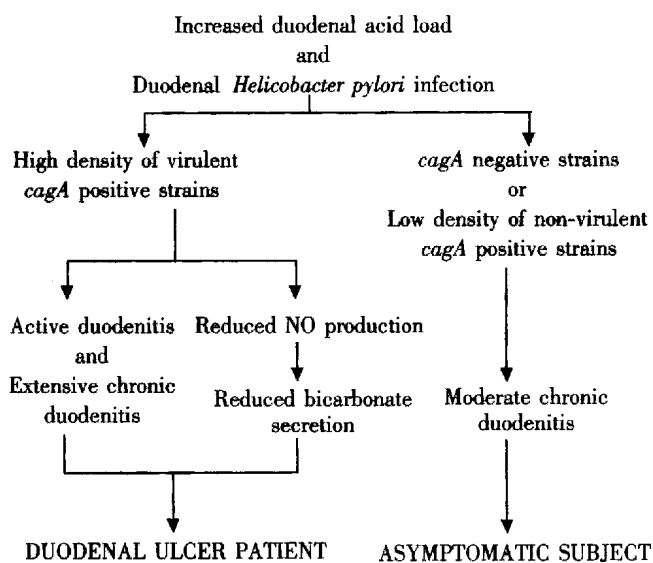
The mechanism by which the *H. pylori* infection is reducing the bicarbonate secretion has been studied recently. The bicarbonate secretion in response to acidification of the duodenal bulb in rats could be inhibited by local administration of a water extract of *H. pylori*<sup>[38]</sup>. In these experiments a substantial increase of the NO synthase inhibitor asymmetrical dimethyl arginine (ADMA) was demonstrated in the duodenal mucosa. Separate administration of ADMA markedly reduced the bicarbonate response to acidification of the bulb. The presence of ADMA has not yet been determined in the bulb mucosa of humans. In the antrum, however, the ADMA concentration was 65 times higher in *H. pylori* infected subjects than in non-infected subjects<sup>[39]</sup>. It is possible that *H. pylori* delivers peptides that are degraded by proteolysis in

the antrum-bulb region to for instance ADMA. It seems reasonable to assume that the high density of *cagA* positive *H. pylori* bacteria in the bulb of DU patients can produce high enough ADMA concentrations to explain the markedly reduced bicarbonate secretion that is a characteristic of DU patients.



**Figure 1** Successive prerequisites for the development of *Helicobacter pylori* induced duodenal ulcer.

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**Figure 2** Conceivable sequence of events in the development of *Helicobacter pylori* induced duodenal ulcer.

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#### WHY DOES ONLY A MINORITY OF *H. PYLORI*/INFECTED SUBJECTS DEVELOP DUODENAL ULCER?

A special series of events seem to result in the development of DU in *H. pylori* infected subjects. The first part of this series of events should be regarded more as a pre-/quisite for the development of DU, and is common for all subjects with an

antrum predominant *H. pylori* gastritis (Figure 1). The antrum gastritis results in hypersecretion of acid, the increased acid load to the duodenal bulb gives rise to formation of GM, and these islands of gastric mucosa can be colonized by *H. pylori*.

The most important factor for the development of DU seems to be a high density of virulent *H. pylori* bacteria in the duodenal bulb. When the density of virulent strains / with *cagA* positivity as a marker of virulence / reaches a high level, two effects are triggered that are characteristic for DU patients. Firstly, a high density of virulent *H. pylori* induces a pronounced release of proinflammatory cytokines, leading to a substantial chronic inflammation and an active duodenitis with its tissue damaging potential. Secondly, a high density of virulent *H. pylori* seems to produce enough amounts of NO synthase inhibitors to significantly reduce the bicarbonate secretion in response to acidification of the duodenal bulb. This entails a high acidity in the bulb leading to a potential increase of GM and tissue damage.

In summary the pivotal components in the conceptual development of DU are hypersecretion of acid and colonization of the duodenal bulb with a high density of virulent *H. pylori* strains resulting in an active duodenitis and reduced bicarbonate secretion (Figure 2).

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