
Conceivable mechanisms by which *Helicobacter pylori* provokes duodenal ulcer disease

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A conceivable concept for the development of duodenal ulcers in *Helicobacter pylori* (*H. pylori*) infected subjects is presented in this chapter. The concept includes an explanation of the fact that only a minority of all *H. pylori*-infected subjects will develop a duodenal ulcer. *Helicobacter pylori* infection of the antrum induces a hypersecretion of gastric acid secretion, giving rise to gastric metaplasia in the duodenal bulb. This gastric metaplasia is a prerequisite for *H. pylori* colonization of the bulb. These events are common to all *H. pylori*-infected subjects. However, a much higher density of *H. pylori* bacteria and colonization with virulent organisms has been found in the bulb of duodenal ulcer patients, resulting in a much stronger inflammatory reaction with active duodenitis and an impaired bicarbonate secretion. These characteristics, together with acid hypersecretion, seem to be the important factors in evoking a duodenal ulcer.

Key words: *H. pylori* infection; duodenal ulcer; hypersecretion of gastric acid; inhibition of gastric acid; gastric metaplasia; duodenal bulb; duodenitis; duodenal bicarbonate secretion.

There are undoubtedly multiple pathogenic mechanisms involved in the development of duodenal ulcer (DU) disease. Hypersecretion of gastric acid is, however, a common denominator. In fact, massive acid hypersecretion can by itself provoke duodenal ulceration, as exemplified by Zollinger–Ellison syndrome. Gastric acid hypersecretion is in all probability a prerequisite in *Helicobacter pylori* (*H. pylori*) induced DU, while the level of acid secretion in the relatively few patients with a non-steroidal anti-inflammatory drug-induced DU is more uncertain. In all three examples, potent anti-secretory treatment can heal the DU disease and prevent its recurrence.

- 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
 - Facilitated gastrin release (reduced somatostatin inhibition)
 - Defective inhibitory mechanisms
 - Antral acidification
 - Antral distension
 - Fat in the duodenum

Figure 1. Gastric acid secretory characteristics of duodenal ulcer patients (all of which might be *H. pylori* dependent).

The gastric acid secretion in DU patients is characterized by several well-established abnormalities (Figure 1). An increased maximal acid secretory capacity has been unequivocally found in about half of all DU patients. The increased maximal acid output is at least partly dependent on an increased parietal cell mass.¹ The maximal acid response to pentagastrin, which is the most commonly used instrument to determine the maximal acid secretory capacity, might also depend on the number of enterochromaffine-like cells and the amount of histamine released from these cells in the vicinity of the parietal cells during pentagastrin stimulation. Furthermore, three physiological inhibitory mechanisms have been found to be defective in DU patients: the inhibition of gastrin release by antral acidification², reflex inhibition by antral distension³, and inhibition by duodenal fat administration (the enterogastron mechanism).⁴ One defective inhibitory mechanism has been found in each group of DU patients so far studied, and it is reasonable to assume – although this has not been studied – that all three are present in every DU patient. The result of these abnormalities is gastric hypersecretion as an increased and/or prolonged gastric acid response to every meal in DU patients.⁵

The most common cause of DU disease is *H. pylori* infection, and successful eradication of the infection will cure the disease. Only a small percentage – about 10–15% – of all those infected will, however, develop a DU. There seems to be a distinct series of events, starting with an antral *H. pylori* infection, that are necessary to result in a DU. The main actors in this series of events are acid hypersecretion, the development of a large area of gastric metaplasia in the duodenal bulb with colonization of *H. pylori* in the bulb, a high density of virulent *H. pylori* bacteria in the bulb with a substantial active and chronic inflammatory response, and a marked *H. pylori*-dependent reduction of bicarbonate secretion in response to acidification of the bulb. The overview will shortly present the evidence for this concept.

HELICOBACTER PYLORI EFFECTS ON GASTRIC ACID SECRETION

In DU patients, the chronic *H. pylori* infection is predominantly located in the antrum. A pronounced *H. pylori* infection of the antrum with an intact parietal cell region will result in acid hypersecretion as a result of a blockade of mechanisms normally

inhibiting acid secretion. It should be emphasized that this hypersecretion of acid exists in all subjects with an antrum-predominant *H. pylori* infection and is thus not a characteristic of DU patients. The *H. pylori*-induced blockade of inhibitory mechanisms leads to a facilitated release of gastrin⁶ but involves also the abolishment of inhibitory reflex pathways from the antrum to the parietal cell region.⁷ However, if the chronic *H. pylori* infection is also pronounced in the parietal cell region, acid secretion will diminish, partly because of a local inhibitory influence of the *H. pylori* infection at the parietal cell level and partly because of a decreased parietal cell mass in the case of atrophic gastritis.⁸

Maximal acid secretory capacity

It is well established that DU patients have a significantly higher maximal acid output in response to histamine and pentagastrin than non-DU subjects, but with a substantial overlap. It has been suggested that the unequivocally increased maximal acid secretory capacity that is to be found in about half of the DU patients might be the result of a genetically determined large parietal cell mass.

It has, however, been shown that half a year after *H. pylori* eradication, the maximal acid response to pentagastrin is significantly reduced in DU patients⁹, although this is not a consistent finding.¹⁰ Since gastrin release is facilitated by antral *H. pylori* infection, a trophic effect of gastrin on the parietal cell region is conceivable. The *H. pylori*-induced increases of basal and meal-stimulated serum gastrin levels are of a moderate magnitude. Similar moderately increased serum gastrin levels are produced by treatment with proton pump inhibitors. Eight weeks of treatment of *H. pylori*-negative subjects with a high dose of omeprazole resulted in a significantly increased maximal acid response to gastrin determined 15 days after the cessation of the omeprazole treatment.¹¹ The result was ascribed to a trophic effect of the moderately increased serum gastrin levels on the parietal cells. Such an interpretation is in agreement with the reduced maximal acid response to pentagastrin after *H. pylori* eradication in the study of Harris et al⁹, as well as with the substantial reduction in the maximal acid response to pentagastrin in DU patients after exact antrectomy leaving the whole parietal cell area intact.¹²

It has also been shown that the eradication of *H. pylori* infection significantly reduces the capacity of pentagastrin to mobilize histamine in the parietal cell region mucosa of DU patients.¹³ The result implies that *H. pylori* infection increases the mobilization of histamine from the enterochromaffine-like cells in the parietal cell region of DU patients, which can contribute to a high maximal acid response to pentagastrin in DU patients.

Why is there such a substantial overlap of the maximal acid outputs in DU patients and non-DU subjects? First, all *H. pylori*-infected subjects, including non-DU subjects, have a facilitated release of gastrin. Second, there is evidence to suggest that glycine-extended gastrins – another product of progastrin than the traditional amidated gastrins – have marked trophic effects but low acid-secretory stimulating activity.¹⁴ Glycine-extended gastrins are released simultaneously with the amidated gastrins from the gastrin-producing G-cells in the antrum, but the two gastrin forms act via different receptors. It is therefore possible that trophic effects and acid-stimulatory effects may differ between subjects depending on the proportion of the two gastrin forms released from the G-cells.

Defective inhibitory mechanisms

A facilitated gastrin release is well established in *H. pylori*-infected subjects, both in the fasting state and in response to meals^{6,15-17}, as well as after stimulation with gastrin-releasing peptide (GRP).^{18,19} The increased release of gastrin was reduced to normal levels after *H. pylori* eradication. The facilitated gastrin release in *H. pylori*-infected subjects is associated with and probably caused by a suppressed action of somatostatin from the antral D-cells.^{20,21} GRP has been used as an experimental instrument to study the effects of *H. pylori* infection on gastrin release and subsequent acid secretion. However, an intravenous infusion of GRP does not necessarily reflect the physiological effects of GRP as a neurotransmitter. Furthermore, GRP releases, apart from gastrin and despite its name, several peptides with an inhibitory effect on acid secretion, for example somatostatin. As expected, GRP-stimulated gastrin and acid secretion are significantly increased in all *H. pylori*-infected subjects, with a normalization after *H. pylori* eradication.¹⁰ The increased acid response to GRP in the *H. pylori*-infected subjects was attributed to a defective inhibition of gastrin release and acid secretion by the suppressed somatostatin function. Most interestingly, the acid response to GRP in *H. pylori*-infected DU patients was about twice that in *H. pylori*-infected non-DU subjects, with a minimal overlap despite similar enhancements of serum gastrin level in response to GRP.¹⁰ A reasonable interpretation is that *H. pylori*-infected non-DU subjects have an increased acid response to GRP as a result of defective inhibitory mechanisms, and that *H. pylori*-infected DU patients have a further increased acid response to GRP due to a reinforced suppression of inhibitory mechanisms. Consequently, *H. pylori*-infected DU patients may have – although this has not been shown – a higher magnitude of acid hypersecretion than *H. pylori*-infected non-DU subjects also under physiological conditions.

Gastric acid secretion is also increased in all *H. pylori*-infected subjects by a defective inhibitory mechanism that is unrelated to endogenous gastrin. Antral distension in healthy subjects without *H. pylori* infection inhibits the gastric acid secretion induced by maximal pentagastrin stimulation. This inhibitory effect is absent in *H. pylori*-infected subjects but appears after eradication of the *H. pylori* infection.⁷ Since the stimulus for acid secretion was a high dose of pentagastrin, the effect of antral distension is obviously independent of any moderate changes in the release of endogenous gastrin. In fact, and unexpectedly, antral distension in DU patients during concomitant intragastric neutralization in order to optimize the release of gastrin did not result in any increase of serum gastrin level.²² The inhibitory effect of antral distension on acid secretion in healthy subjects without *H. pylori* infection is in all probability caused by an inhibitory reflex pathway from the antrum to the parietal cell region. The *H. pylori* infection blocks this inhibitory reflex, resulting in a suppressed inhibition of acid secretion. The transmitter mechanisms affected by the impaired reflex inhibition from the *H. pylori*-infected antrum are unknown, but the final link in the reflex chain may be located at the enterochromaffine-like and/or parietal cell level.

Defective inhibitory mechanisms caused by antral *H. pylori* infection, including a facilitated release of gastrin and a blockade of the inhibitory reflex pathways, should be operating under physiological conditions, i.e. during and after meals. An increased release of gastrin during meals in *H. pylori*-infected subjects is well established.^{6,15-17} The gastric acid response to a peptone meal of pH 7.0 was shown to be about twice as high and prolonged in *H. pylori*-infected subjects compared with non-infected healthy subjects.¹⁷ The hypersecretory acid response to the meal was normalized after

eradication of the *H. pylori* infection. An increased release of gastrin in *H. pylori*-infected subjects has also been shown during meals with an acidified antrum.^{16,17} After an acidified meal of pH 2.0, there was a significantly higher gastrin release and acid response in *H. pylori*-infected subjects compared with non-infected subjects, again with a normalization of both parameters after *H. pylori* eradication.¹⁷ The well-known mechanism by which acidification of the antrum inhibits gastrin release and the gastric acid response to gastrin is thus clearly impaired in *H. pylori*-infected subjects. The increased gastric acid responses to neutral and acidified meals in *H. pylori*-infected subjects could not, however, be explained entirely by the increased release of gastrin.¹⁷ It is therefore reasonable to assume that other defective inhibitory mechanisms, for example the impaired inhibitory distension reflex from the antrum to the parietal cell region⁷, must contribute. The inhibitory enterogastrone mechanism is defective in DU patients³, but whether this inhibitory mechanism is also blocked by *H. pylori* infection has not been ascertained.

In summary, antral *H. pylori* infection causes gastric acid hypersecretion by a blockade of physiological inhibitory mechanisms, resulting in an increased and prolonged acid response to meals. At least in the experimental situation of intravenous GRP stimulation, the acid hypersecretion is accelerated in DU patients. The final result is an increased duodenal acid load in subjects with an antral *H. pylori* infection.¹⁷

GASTRIC METAPLASIA

Gastric metaplasia (GM) of the duodenal bulb is a prerequisite for *H. pylori* colonization of the bulb. GM develops in response to an increased duodenal acid load, and extensive gastric metaplasia has been found in the duodenum of patients with Zollinger–Ellison syndrome.²³ GM has been found at a high frequency in *H. pylori*-infected subjects, with a prevalence of about 90% in DU patients and about 60% in non-DU subjects^{24–26}, both groups having an increased duodenal acid load. It has, however, been proposed that a severe inflammation of the GM islands caused by *H. pylori* may further increase the extent of GM primarily induced by acid hypersecretion.²⁷ The concept that the extent of GM is partly dependent on the *H. pylori*-activated inflammatory process in the GM has been supported by the finding that the combination of *H. pylori* eradication and acid suppression produced a greater reduction in GM than either treatment alone.²⁸

Antral *H. pylori* infection results in a hypersecretion of acid and a high prevalence of GM in both DU patients and non-DU subjects, albeit with some preponderance in DU patients. It therefore seems reasonable to assume that a critical factor in the development of DU may be a high number of *H. pylori* bacteria and/or particularly virulent strains of *H. pylori* in the duodenal bulb. The aim of a recent study was systematically to determine the extent of GM, the quantity and the cytotoxin-associated gene A (*cagA*) status of *H. pylori*, and the severity of inflammation in biopsies from both the antrum and the duodenal bulb in DU patients and asymptomatic infected subjects.²⁶ Such comparisons of *H. pylori* status and degree of inflammation between the antrum and duodenal bulb in the same subject, and between DU patients and non-DU subjects, have not previously been undertaken. The extent of GM had to be carefully determined to make a meaningful comparison of the other parameters between the DU and non-DU subjects. Since GM is patchy and as yet cannot be visualized during endoscopy, a high number of biopsies had to be taken from the duodenal bulb: two

from each quadrant. The extent of GM was almost four-fold greater in the *H. pylori*-infected DU patients compared with the *H. pylori*-infected non-DU subjects.²⁶

BACTERIAL DENSITY AND CAGA STATUS IN THE DUODENAL BULB

A very high prevalence of *H. pylori* has been found in the duodenal bulb of both DU patients (95%) and infected non-DU subjects (80%)²⁶, suggesting that colonization of GM in the bulb is a common phenomenon. Rigorous precautions were taken to avoid contamination of the duodenal biopsies by *H. pylori* from the stomach during endoscopy. Therefore, the high prevalence figures of *H. pylori* in the duodenal bulb in all probability represent a true colonization of the bulb and were the results of the sensitive technique of quantitative culture.²⁹ It seems, however, that a certain *H. pylori* density in the antrum – about 10^4 colony-forming units in a biopsy – is required for colonization of the bulb to occur.²⁶ Lewis antigens on *H. pylori* lipopolysaccharides may contribute to permanent colonization by facilitating the attachment of *H. pylori* to gastric or metaplastic epithelium³⁰, and by allowing *H. pylori* to escape from host responses. *H. pylori* strains from the duodenal bulb expressed Lewis antigens in 90% of DU patients and only 42% of non-DU subjects.³¹

The *H. pylori* density in the duodenal bulb was much lower than in the antrum, even after correction for the area of GM²⁶, suggesting that the duodenum constitutes a less favourable environment for colonization with *H. pylori*. However, the mean density of *H. pylori* in the duodenal bulb was 20 times higher in DU than in non-DU subjects²⁶ despite the fact that the *H. pylori* density in the antrum was the same in the two groups, yet there was a considerable overlap in the duodenal *H. pylori* density between DU patients and non-DU subjects. It has been shown that *cagA* positivity is related to the density of *H. pylori* in the antrum.^{29,32} Similarly, it was found that subjects with *cagA*+ strains in the duodenal bulb had a 10-fold higher *H. pylori* density in the bulb than did subjects with *cagA* strains.²⁶

An association between *H. pylori*-induced DU and *cagA* positivity has frequently been observed, but in several reports there has been no significant difference in the prevalence of *cagA* strains in the antrum between DU patients and non-DU subjects. It appears that *cagA* positivity is a marker for a more virulent group of *H. pylori* strains possessing a cluster of additional genes encoded by a pathogenicity island.^{32,33} Some of these additional genes in *cagA* strains induce pro-inflammatory cytokines with mucosa-damaging potential.³⁴ It should be emphasized that multiple strains, including *cagA* and *cagA* strains, can exist in the same subject.^{26,35,36} Since, at least in the duodenal bulb, colonies from each biopsy always showed the same *cagA* status²⁶, it is necessary to culture from multiple biopsies to determine the predominant strain. Therefore the proportion of *cagA*-positive bacteria in relation to the total number of organisms may be an important factor determining the local damaging potential of *H. pylori* colonization.

A new and significant finding was the fact that DU patients had a much higher prevalence of *cagA*+ *H. pylori* strains in the duodenal bulb (81%) than did *H. pylori*-infected non-DU subjects (30%), despite a marginal difference in the prevalence of *cagA*+ strains in the antrum of the same subjects (86% versus 75%).²⁶ Consequently, the GM environment in the duodenal bulb seems to constitute a separate entity disengaged from the conditions in the gastric antrum for permanent *H. pylori* colonization.

HELICOBACTER PYLORI-INDUCED INFLAMMATION IN THE DUODENAL BULB

The inflammatory cells are found in association with areas of GM. Chronic duodenitis, determined by scoring the lymphocytic infiltration, was more marked in *H. pylori*-infected DU patients than in *H. pylori*-infected non-DU subjects but again with a considerable overlap.²⁶ Positive mutual relations were found between the extent of GM, the bacterial density and the chronic inflammatory score.²⁶

Active duodenitis, defined by the presence of neutrophils, is a common finding in DU patients. In a recent study of *H. pylori*-infected DU patients and non-DU subjects, active duodenitis was found only in DU patients and almost exclusively in DU patients with *cagA*+ strains in the duodenal bulb.²⁶ *CagA*+ strains induce much higher levels of the pro-inflammatory cytokine interleukin 8 (IL-8) in gastric epithelial cells in vitro than do *cagA*- strains.^{34,37} *CagA*+ strains have also induced an increased inflammation in the gastric mucosa in vivo, at least partly because of the activation of IL-8.³⁸ Close contact between the *H. pylori* and gastric epithelial cells seems to be necessary for inducing a substantial IL-8 response^{34,37} since culture supernatant and non-living *H. pylori* did not produce any significant response. However, disruption of the *cagA* gene did not reduce the IL-8 activation in gastric epithelial cells.³⁹ Instead, the *picB* gene, located in the vicinity of the *cagA* gene, seems to be needed for IL-8 induction.⁴⁰ The *picB* gene is invariably linked with *cagA*, and the *cagA*-*picB* gene cluster constitutes a large pathogenicity island unique to *cagA*+ strains and responsible for IL-8 induction.³³ *CagA*+ is thus a marker for virulence, but its own function is unknown. The combination of *cagA*+ strains, the *picB* gene and IL-8 production, together with a high duodenal acid load, forms a conceivable trigger mechanism for tissue damage and ulcer formation in the duodenal bulb. IL-8 provokes the accumulation and activation of neutrophils capable of releasing proteolytic enzymes with tissue-damaging potential⁴¹, as well as inducing reactive oxygen metabolites in gastric epithelial cells⁴², with an additional tissue-damaging effect.

BICARBONATE SECRETION IN THE DUODENAL BULB

A high duodenal acid load has the potential to damage the mucosa in the duodenal bulb. The first line of defence against luminal acidity is increased duodenal bicarbonate secretion in response to the acidification. The bicarbonate will neutralize the acid, forming carbon dioxide and water. It is now established that the duodenal bicarbonate secretion in response to acidification is a nitric oxide (NO) dependent mechanism. The NO synthase inhibitor L-NAME, administered into the duodenal perfusate of rats, blocked the bicarbonate response to acidification.⁴³ Furthermore, acidification of the proximal duodenum of pigs resulted in a simultaneous increase of bicarbonate secretion and NO production that was determined directly by chemiluminescence.⁴⁴ Both responses were inhibited by the intraluminal administration of the NO synthase inhibitor L-NMMA, the inhibitory effect of which could be reversed by the administration of the normal substrate L-arginine. Carbon dioxide seems to be the mediator of the duodenal bicarbonate response to acidification since a high carbon dioxide tension in a neutral duodenal perfusate stimulated the bicarbonate secretion, and this response could be blocked by a NO synthase inhibitor.⁴⁵ The presence of inducible NO synthase immunoreactivity has recently been demonstrated in the duodenal mucosa, being found to be most prominent at the tips of the villi.⁴⁶ Duodenal

acidification produced a marked increase of this NO synthase expression. Furthermore, the bicarbonate response to duodenal acidification could be blocked by a selective inhibitor of inducible NO synthase. In summary, it seems that duodenal acidification via carbon dioxide activates inducible NO synthase in the epithelial cells and that the resulting NO stimulates the bicarbonate secretion.

DU patients have impaired bicarbonate secretion in response to acidification of the duodenal bulb.⁴⁷ The defective bicarbonate response to duodenal acidification in DU patients has been found to be dependent on the presence of *H. pylori* infection since the bicarbonate response was normalized after *H. pylori* eradication.⁴⁸ It was also shown that the bicarbonate response to duodenal acidification was not significantly impaired in *H. pylori*-infected non-DU subjects. Consequently, it seems that the impairment of the bicarbonate response to duodenal acidification caused by *H. pylori* infection is a characteristic of DU patients.

The mechanism by which *H. pylori* infection interferes with duodenal bicarbonate secretion has been the subject of recent studies. Water extracts of *H. pylori* bacteria administered to the duodenal perfusate in rats have been shown to abolish the bicarbonate response to acidification.⁴⁹ The bicarbonate response in these experiments was normalized after administration of the NO synthase substrate L-arginine to the duodenal perfusate, suggesting that the *H. pylori* bacteria interfered with the NO synthase activity in the duodenal epithelial cells. Furthermore, the concentration of the endogenous NO synthase inhibitor asymmetric dimethyl arginine (ADMA) was markedly increased in both the duodenal perfusate and the duodenal tissue after exposure to the *H. pylori* extract. The proteolysis of *H. pylori* was shown to produce ADMA, and substituting the *H. pylori* extract for ADMA in the duodenal perfusate also blocked the bicarbonate response to duodenal acidification. The mucosal concentrations of L-arginine and ADMA have been determined in the antrum of *H. pylori*-infected and non-infected subjects. L-arginine concentrations were about the same in both groups, while the ADMA concentrations were about 65 times higher in the antral mucosa of *H. pylori*-infected subjects.⁵⁰ It would be most interesting to study whether the same is true for the duodenal mucosa, and whether *cagA*+ strains of *H. pylori* are particularly effective in producing ADMA. It seems reasonable to assume that *H. pylori* – dead or alive – deliver peptides that, in the antrum and duodenal bulb, are degraded by proteolysis to various amino acid residues, including the NO synthase inhibitor ADMA. The presence of *H. pylori*-induced ADMA could interfere with NO synthase in the duodenal epithelial cells and contribute to an impairment of the bicarbonate response to duodenal acidification. Speculatively, the high density of *cagA*+ strains of *H. pylori* in the duodenal bulb of DU patients might explain the impaired bicarbonate response to duodenal acidification that is a characteristic of DU patients.

WHY DOES DUODENAL ULCER DEVELOP IN ONLY A MINORITY OF HELICOBACTER PYLORI-INFECTED SUBJECTS?

Although there is no definite answer to this question at present, evidence is accumulating to show a conceivable chain of events leading to a DU in a *H. pylori*-infected subject. The *H. pylori* infection in the antrum creates the necessary conditions by inducing gastric acid hypersecretion as a result of an interference with mechanisms normally inhibiting gastrin release and acid secretion. The resulting increased duodenal acid load gives rise to islands of gastric metaplasia in the duodenal bulb, which then can

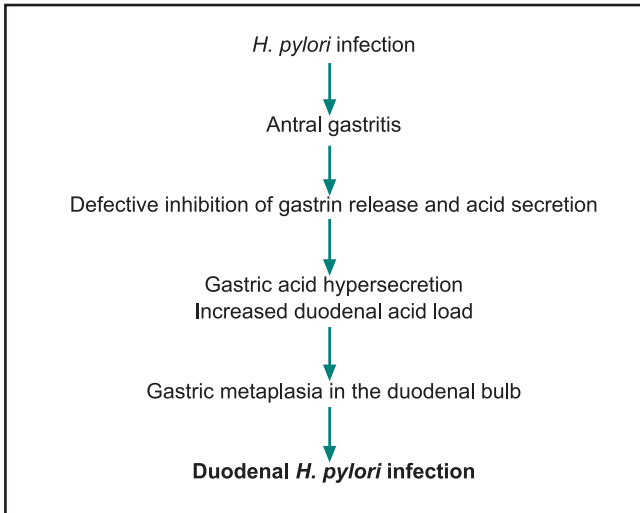


Figure 2. Successive prerequisites for the development of *H. pylori*-induced duodenal ulcer.

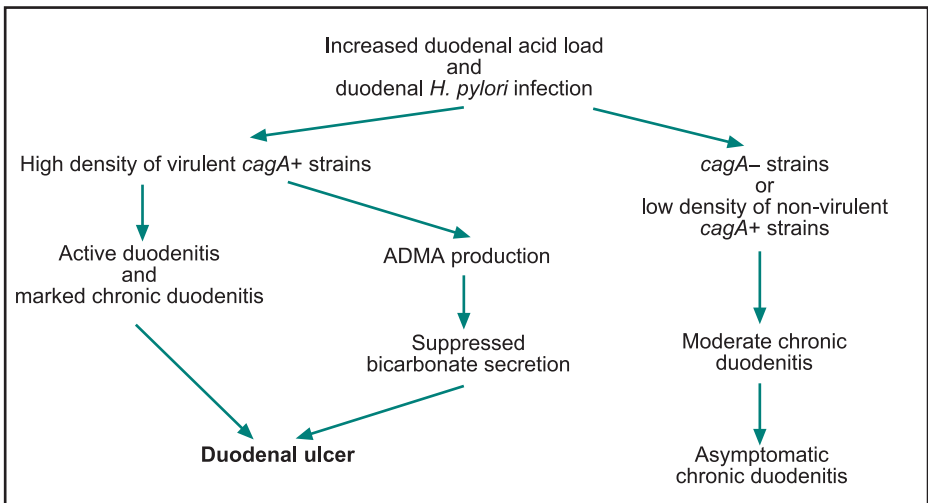


Figure 3. Conceivable sequence of events in the development of *H. pylori*-induced duodenal ulcer.

be colonized by *H. pylori*. The sequence of events is, however, common to all *H. pylori*-infected subjects (Figure 2).

A critical factor in the development of a duodenal ulcer seems to be the quantity of virulent *H. pylori* strains in the duodenal bulb. When the quantity of virulent bacteria is high enough, another series of events is provoked, leading to a DU. In fact, DU patients have a much higher density of virulent *H. pylori* bacteria in the duodenal bulb – with *cagA* positivity as a marker for virulence – than do *H. pylori*-infected subjects without a DU. This higher density of virulent organisms in the bulb gives rise to two effects characteristic for DU patients. First, the comparatively large number of

virulent bacteria induces a substantial release of particularly pro-inflammatory cytokines, resulting in a much stronger inflammatory reaction than in infected non-DU subjects, with a higher degree of chronic inflammation and an active duodenitis with neutrophil infiltration, the latter being unique for DU patients. The neutrophil infiltration may cause a further increase of the gastric metaplastic area in the bulb and entails a marked potential for tissue damage. Second, it seems probable that the high density of virulent *H. pylori* bacteria in the bulb of DU patients produces a sufficiently high concentration of the NO synthase inhibitor ADMA to substantially impair the NO dependent bicarbonate response to duodenal acidification. This means a higher degree of acidity in the bulb of DU patients, in turn leading to a larger area of GM and to an increased potential for tissue damage. In summary, a conceivable concept for development of a DU in *H. pylori*-infected subjects involves the hypersecretion of gastric acid and a sufficient number of virulent strains colonizing the duodenal bulb, followed by an active duodenitis and impaired bicarbonate secretion in the bulb (Figure 3).

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