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Immune Response in *Helicobacter pylori* Infection

Implications for Treatment of Gastroduodenal Disease

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Summary

Since the discovery of *Helicobacter pylori* our views concerning the pathogenesis and treatment of gastroduodenal disease have changed dramatically. Most individuals infected with this organism remain asymptomatic throughout life. However, some manifest clinical disease, such as gastric and duodenal ulcer. Recently results have also implicated *H. pylori* infection in the development of gastric lymphoma of mucosa-associated lymphoid tissue and gastric cancer. Variations of an individual's immune response based on inheritance, age or environmental factors could explain the diverse clinical outcomes of the infection. However, our understanding concerning these mechanisms is still very incomplete.

Marked neutrophilic infiltration within the gastric mucosa induced by bacterial components may account for acute mucosal damage. Chronic infection is accompanied by T cell and B cell infiltration into lymphoid follicles, which could contribute to atrophy and malignant transformation of glandular epithelium.

Antimicrobial therapy can eradicate the organism, thus alleviating the host's immune response. More efficient treatment regimens such as the combination of the proton pump inhibitor omeprazole with amoxicillin are now being used. These combinations have fewer adverse effects and improve patient compliance.

Oral vaccines may be useful for the prophylactic treatment of large populations in whom the incidence of *H. pylori* infection is especially high. The scarcity of

studies on vaccine development may be attributed to 3 factors: (a) lack of knowledge of suitable immunogens for immunisation; (b) lack of appropriate animal models; (c) the poorly characterised cellular immune response towards specific antigens of the organism. Further research into the immunopathogenesis of *H. pylori*–related disease is necessary.

For a long time it was an accepted fact that gastric acid secretion did not permit long term bacterial colonisation of the stomach. Although several investigators from as early as 1906 had described the presence of spiral organisms in close contact with human gastric mucosa,[1,2] it was the first identification of *Helicobacter* (formerly *Campylobacter*) *pylori* in human gastric mucosa by Warren and Marshall in 1983[3] that demonstrated that long term colonisation by a human bacterial pathogen was possible. *H. pylori* colonisation of gastric mucosa is now appreciated as one of the most common bacterial infections in humans, and has been shown to be the causative agent of chronic active type B gastritis. Furthermore, it is closely associated with peptic and duodenal ulcer disease,[4-7] and, as recent data suggest, with gastric carcinoma.[8,9] However, most individuals with *H. pylori* infection remain asymptomatic, although chronic inflammatory changes always occur and chronic atrophic gastritis and intestinal metaplasia may develop after many years of infection.[10]

Our understanding of how chronic infection by this pathogen may lead to such a diverse clinical outcome is still very incomplete. Two explanations have been proposed. First, genetic diversity of virulence factors and antigenic profiles of various *H. pylori* strains may account for different disease entities. Secondly, genetically based differences in the individual's immune response towards the pathogen may result in failure to eradicate the infection, leading to chronic mucosal damage. This review considers the latter aspect and attempts to evaluate present knowledge concerning the host's immune response towards *H. pylori* and how it is affected by modern treatment regimens.

1. Clinical Disease is a Consequence of Host Immune Response

1.1 Features of Infection with *Helicobacter pylori*

Infection with *H. pylori* probably occurs via oral ingestion of the bacterium.[11,12] *H. pylori* has developed an array of virulence factors that permit colonisation and survival in a hostile environment such as the stomach. These include:

- enhanced motility[13]
- production of adaptive enzymes such as urease[14,15]
- specific adherence to gastric epithelial cells.[16]

Rapid movement through the gastric mucus because of its spiral shape and presence of flagella allows the bacterium to reach specific attachment sites on epithelial cells. Recently, adherence of *H. pylori* mediated by the Lewis^b (Le^b) blood group antigen has been demonstrated.[17]

The bacterium itself may be a source of specific toxins or products that promote direct mucosal damage. An 87kD vacuolising cytotoxin[18] was detected more frequently in isolates from *H. pylori*–infected peptic ulcer patients than from infected patients with gastritis only.[19] The enzyme phospholipase A found in *H. pylori* filtrates degrades gastric mucus, leading to the formation of lysophospholipids that seriously impair the protective function of the mucus gel.[20]

It is known that various enteropathogenic bacteria (e.g. *Salmonella, Shigella* and certain types of *Escherichia coli*) may enter the epithelial cell itself or traverse the epithelial barrier.[21] This does not seem to be the case in *H. pylori* infection. Although some electron microscopic studies have shown the sporadic occurrence of the organism intercellularly beneath tight junctions[22] and within the lamina

propria,[23] the invasive capacity of *H. pylori* is considered to be low. Its preferred location seems to be within the gastric pits close to the epithelial cell surface, without evidence of direct damage to epithelial cells.[24]

1.2 Markers of Active Inflammation

The initial immune response to infection is characterised by the marked accumulation of polymorphonuclear neutrophils in mucosal tissue, a feature which is termed 'activity' of inflammation. Histopathological examination of diseased gastric mucosa reveals a pronounced association between the density of bacterial colonisation and the intensity of neutrophil infiltration. This is reflected by the close topographic association between the presence of *H. pylori* and the degree of inflammatory activity seen in individual biopsy specimens.[25,26]

Since the bacterium is presumed to be a non-invasive pathogen, the mechanism of inflammation is probably that enhanced mucosal permeability as a result of infection causes certain protein components and secreted products of the organism to traverse the epithelial barrier. This directly or indirectly causes activation of leucocytes and their enhanced local migration into mucosal tissue. The mechanism of leucocyte recruitment may involve 2 pathways. First, direct interaction of the bacterium with gastric epithelial cells leads to an enhanced release of neutrophil chemotactic factors and cytokines. Secondly, *H. pylori* proteins may exhibit direct chemotactic activity on neutrophils and mononuclear leucocytes (fig. 1).

1.2.1 Host Chemotactic Factors

Potent lipid mediators are known to be released by mucosal tissue upon contact with intestinal bacteria.[27] Platelet-activating factor (PAF) is a potent chemotactic factor for neutrophils and eosinophils, and has a wide range of other immunomodulatory actions including effects on lymphocyte proliferation. PAF shows strong ulcerogenic properties in the stomach,[28] and seems to mediate gastrointestinal damage associated with endotoxic shock.[29] *H. pylori* itself produces a PAF acether.[30]

The leukotrienes are another group of lipid mediators for granulocyte recruitment into the mucosa. Leukotriene B_4 is a specific chemotactic factor for neutrophils and has been shown to be produced in rat gastric mucosa.[31] The peptidoleukotrienes (C_4, D_4 and E_4) are chemotactic for eosinophils. It is known that bacterial formylated peptides are potent stimuli for leukotriene synthesis within the mucosa.

So far, only one mucosal neutrophilic chemotactic factor, the neutrophil-activating protein (NAP-1) or interleukin (IL)-8, has been investigated in *H. pylori*–associated gastritis. Crabtree et al.[32] showed IL-8 secretion to be significantly enhanced in 24-hour organ cultures of *H. pylori*–infected gastric mucosa. IL-8 levels correlated well with gastritis activity (neutrophil infiltration) and grade of surface degeneration. However, since activated neutrophils may also secrete IL-8 it is not certain whether increased IL-8 levels simply reflect the density of neutrophil infiltration or are truly of mucosal origin.

1.2.2 Bacterial Chemotactic Factors

There is increasing evidence that extracts or sonicates of *H. pylori* may directly influence neutrophil activity. Products of bacterial origin that may activate neutrophils include *N*-formylmethionyl-leucyl-phenylalanine (FMLP) and related peptides,[33] endotoxin and bacterial sonicates.

Supernatant and washed cell preparations of *H. pylori* isolates can significantly stimulate the oxidative burst response of human peripheral blood granulocytes.[34-36] When the cells are opsonised with complement-inactivated human anti–*H. pylori* plasma this reaction is potentiated. It has been suggested that FMLP-containing fractions in these supernatants could account for the neutrophil activation seen. This would imply that *in vivo* FMLP traverses the gastric barrier and escapes inactivation by degrading enzymes. However, normal colon mucosa is almost impermeable to FMLP, and high activities of the degrading enzyme carboxypeptidase C have been found in the small intestine.[37]

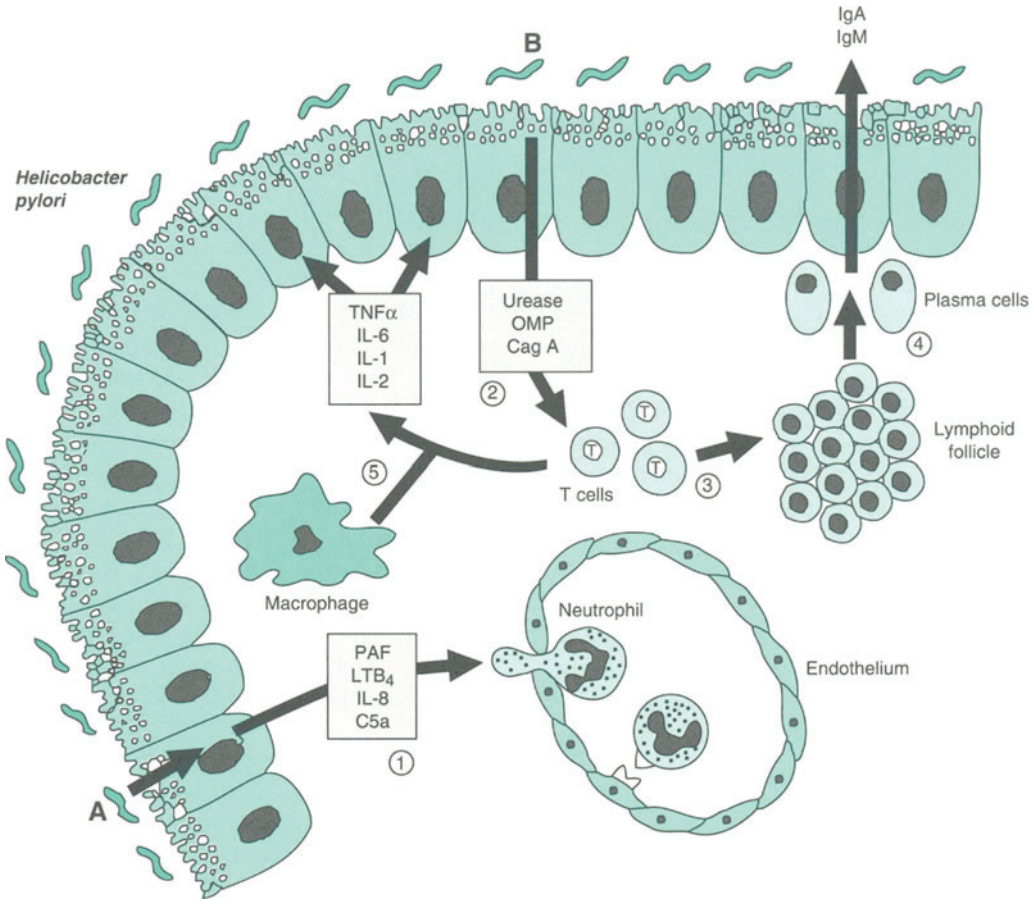

Fig. 1. Scheme depicting suggested mechanisms involved in the local immune response in *Helicobacter pylori*–associated gastritis. (**A**) Bacterial products or components may directly stimulate the epithelium to produce chemoattractants (1) leading to enhanced granulocyte adherence to the endothelium (e.g. via the interaction of CD11b/CD18 and intercellular adhesion molecule-1) and extravasation into the lamina propria. (**B**) Products or components (2) may traverse the epithelial barrier and stimulate granulocytes, macrophages and T and B lymphocytes. CD4+ T cells provide help to B cells (3), promoting their differentiation into plasma cells (4) which produce specific IgM and IgA antibodies. These may be secreted into the gastric lumen coupled to secretory component. Lymphocytes and macrophages may secrete pro-inflammatory cytokines (5) leading to further recruitment of immune cells and possibly direct epithelial perturbation. *Abbreviations:* C5a = complement component 5a; Cag A = cytotoxin-associated gene A; IL = interleukin; LTB_4 = leukotriene B_4; OMP = outer membrane proteins; PAF = platelet-activating factor; TNFα = tumour necrosis factor-α.

In contrast, others[36,38] have identified a 25 to 35kD chemotactic polypeptide present in *H. pylori* sonicates that was nondialysable, heat-stable (to 56°C) and ammonium sulphate precipitable. This polypeptide was able to enhance the oxidative burst response of granulocytes and caused increased migration of both neutrophils and monocytes *in vitro*. This suggests that *N*-formyl oligopeptides are not the active chemotactic factors in *H. pylori* preparations.

Studies by others[39] and our group (W.P. Brooks et al., unpublished work) investigating the expression of adhesion molecules on the surface of granulocytes seem to confirm this finding. Water-soluble *H. pylori* extracts upregulate the expression of the β_2-integrin complex CD11b/CD18 on

the neutrophil surface. This enhances the adhesion of granulocytes to endothelial cells via the counter-receptor intercellular adhesion molecule-1 (ICAM-1), which is present on activated endothelium in *H. pylori*–associated gastritis.[40] This process may be responsible for the extravasation of neutrophils into the lamina propria of mucosal tissue. Characterisation of the active component within the extract showed it to be a polypeptide lying within a molecular weight range of 30 to 100kD.

The significance of *H. pylori*–mediated granulocyte activation lies in the potential of triggered neutrophils to induce direct mucosal damage. They generate toxic oxidants such as superoxide, hydrogen peroxide and hypochlorous acid which, if overproduced, lead to cellular damage.[41] Suzuki et al.[42] used a cytotoxicity assay with cultured rabbit gastric mucosal cells to demonstrate considerable epithelial cell injury when *H. pylori*–activated neutrophils were added to the culture dish. Neither *H. pylori* nor neutrophils alone produced significant epithelial cell injury in this system. Scavengers of reactive oxygen metabolites such as catalase and taurine decreased both the elevated chemiluminescence activity and the aggravated gastric mucosal cell injury produced by *H. pylori*–activated neutrophils. This suggests that the highly toxic compound monochloramine might play an important role in inducing injury, since both scavengers inhibit monochloramine production.

1.3 Markers of Chronic Inflammation

Little is known concerning the pathogenic mechanisms involved in the induction and maintenance of the specific immune response toward *H. pylori* infection. Most of our knowledge is descriptive in nature. For the pathologist, 'chronicity' of infection, as opposed to 'activity' (of neutrophils), is evaluated by the intensity of mononuclear cell infiltration in the mucosa. This indicates the 'grade' of gastritis. There is a close correlation between the prevalence of lymphoid follicles and lymphoplasmocellular infiltrates and the density of *H. pylori* colonisation.[43] These changes are unique to *H. pylori*–associated chronic gastritis and are not seen in other types of gastritis, such as reflux gastritis.

1.3.1 Lymphoid Follicles and Gastric Lymphoma

Lymphoid follicles are never found in normal gastric mucosa, as opposed to the small intestine and colon. The follicles are composed of a B cell–rich centre surrounded by CD4+ T helper cells, CD45RO+ memory cells, and human mucosal lymphocyte-1 T cells (fig. 1).[44,45] The presence of these follicles has prompted much discussion as to their possible significance as precursors in the development of gastric mucosa-associated lymphoid tissue (MALT) lymphoma.

Over 92% of patients with a gastric MALT lymphoma have active *H. pylori* infection.[46] Especially in the early stages of the disease the diagnosis of low-grade MALT lymphoma may be difficult, since in *H. pylori*-associated gastritis reactive lymphoid infiltrates are often seen deep within the mucosa where they can disrupt the glands, the so-called lymphoepithelial lesions.[46-48] Tumour cells obtained from low-grade gastric B cell lymphomas containing neoplastic B cells and non-neoplastic T cells proliferate in the presence of stimulating strains of *H. pylori*.[49] Removal of T cells from the cell suspension results in a decrease in proliferation and IL-2 receptor expression. No responses are seen in cells from high-grade gastric MALT lymphoma or low-grade B cell MALT lymphomas of other sites. Treatment to eradicate *H. pylori* may lead to regression of low-grade B cell gastric MALT lymphomas.[50]

1.3.2 Stimulation of Lymphocytes by Bacterial Antigens

The findings above demonstrate the possible significance of antigen-specific T cell and B cell recognition in *H. pylori*–associated disease. The presence of non–intestine-derived memory T cells within *H. pylori*–associated lymphoid infiltrates reflects immigration and local activation of T cells. Initially this has prompted investigations into potentially immunogenic bacterial antigens and their interactions with peripheral blood lymphocytes.

Whole inactivated *H. pylori* suspensions stimulate blood mononuclear cells from individuals with and without IgG antibodies to *H. pylori* components, but antibody-positive individuals tend to have lower proliferative responses.[51,52] In the presence of mitogens these suspensions significantly suppress proliferative responses in both *H. pylori*–positive patients and *H. pylori*–negative healthy control individuals.[53] It has been suggested that nonspecific suppression of monocyte activity, rather than a specific T cell effect, is responsible for this immunosuppressive phenomenon on mitogenic proliferation.

However, other investigators[54,55] have shown activation of peripheral blood mononuclear cell suspensions by *H. pylori* extracts. Whole *H. pylori* antigen and *H. pylori* lipopolysaccharide cause monocyte activation by inducing the expression of the monocyte surface antigen HLA-DR and of IL-2 receptors, production of the inflammatory cytokines IL-1 and tumour necrosis factor, and secretion of the reactive oxygen intermediate superoxide anion.

1.3.3 Humoral Immune Response

An intense humoral systemic immune response can be detected in *H. pylori*-infected patients, all of whom show high antibody titres of the IgG and IgA subclasses.[56] Increased activity of gastritis in *H. pylori* infection correlates well with high serum IgG antibody titres. Specific IgG antibody levels decline after antibacterial treatment and eradication of the bacterium, reflecting therapeutic success.[57]

However, responses seen in peripherally derived mononuclear cell suspensions and serum do not necessarily mirror the local specific immune response at the mucosal level. The mucosal immune system differs substantially from the systemic immune system in that immune processing within the mucosa usually results in unresponsiveness towards luminal antigen.[58,59] When a response does occur, T helper cells (CD4+ T cells) recognise antigen via a specific receptor in conjunction with the expression of the major histocompatibility antigen (MHC) class II molecule present on antigen-presenting cells (e.g. macrophages, dendritic cells, epithelium). T helper cells preferentially help or trigger mucosal B cells to produce a specific IgA response towards the presented antigen.

In *H. pylori*–associated gastritis, there is strong expression of aberrant HLA-DR molecules (human MHC class II) on gastric epithelial cells that are in close proximity to mononuclear infiltrates.[60-62] There is also a direct correlation between the degree of HLA-DR activation and the number of activated T cells.[63] A marked local IgA response with increased synthesis of secretory component may be detected within infected regions of the stomach.[64] The presence of specific mucosal IgA antibodies toward the *H. pylori* 120kD protein is positively correlated with peptic ulceration.[65] Because secretory IgA has no opsonic activity and cannot activate complement, IgA-coated bacteria may, in fact, escape phagocytosis, contributing to their survival. On the other hand, specific secretory IgA antibodies in human colostrum inhibit cell-specific attachment of *H. pylori* to human gastric surface mucous cells,[66] which subsequently protects infants from early acquisition of the infection.[67]

The unusually high levels of specific IgG antibodies against *H. pylori* may facilitate killing of bacteria by opsonisation and neutrophil activation. However, at the same time, they may induce gastric epithelial damage by promoting the release of inflammatory mediators such as C5a and PAF. Furthermore, IgG antibodies of *H. pylori*-positive individuals show crossreactivity with mucus and foveolar epithelium in corpus and antrum,[68] suggesting that an autoimmune component may be involved in mucosal perturbation.[69-72]

2. Implications for Treatment

2.1 Antimicrobial Chemotherapy

Since the introduction of H_2-receptor antagonists in 1976, standard ulcer treatment has been based on the fundamental observation 'no acid, no ulcer'. Suppression of gastric acid secretion by H_2-

receptor blockers will lead to ulcer healing in a high proportion (80 to 90%) of patients after a treatment course of 8 to 12 weeks.[73] However, such therapy does not alter the natural history of peptic ulcer disease, reflected by the fact that discontinuing H_2-blocker therapy will lead to ulcer relapse in approximately 80% of patients within 1 year.[74-77]

A different more causal approach in peptic ulcer treatment could be eradication of *H. pylori*. Although *H. pylori* is sensitive to many antibacterials *in vitro*,[78-80] including aminoglycosides, ampicillin, cephalosporins, macrolides, nitroimidazoles, penicillins, quinolones and tetracyclines, eradication *in vivo* has proven quite difficult. Monotherapy with these agents leads to eradication rates not above 20% and may result in antimicrobial resistance, particularly when macrolides, nitroimidazoles or quinolones are used.

The first studies of combined use of at least 2 antibacterials led to eradication rates of up to 70% and relapse rates of 21%.[81] Relapse occurred primarily in patients in whom *H. pylori* persisted. Many of the early eradication regimens employed bismuth compounds, usually colloidal tripotassium dicitratobismuthate (bismuth subcitrate) or bismuth salicylate, and a nitroimidazole (e.g. metronidazole or tinidazole). Bismuth salts are active within the gastric lumen and precipitate in and around *H. pylori* organisms in the gastric mucus layer, leading to their detachment from the epithelium and subsequent lysis within 2 hours of ingestion.[82]

Numerous studies of eradication of *H. pylori* have been completed.[83-100] Triple therapy with bismuth compounds plus 2 antibacterials achieves high eradication rates of up to 90% if the *H. pylori* strain is susceptible to the nitroimidazoles used in most of the regimens,[83-86] but only 30 to 60% if the strains are resistant. Although nitroimidazoles show excellent activity against *H. pylori in vitro*, primary *H. pylori* resistance against metronidazole has been found in 11 to 95% of patients.[87-89] An even greater problem of treatment regimens using nitroimidazoles is secondary resistance, which develops under treatment in approximately 2 to 9% of patients. It has been reported that combination of nitroimidazoles with bismuth salts reduces primary nitroimidazole resistance from 70% in patients treated without bismuth to 9% in those treated with bismuth,[88] but resistance still remains a problem of all triple therapy regimens involving nitroimidazoles.

Two other major difficulties have become evident from studies with the otherwise highly effective triple therapy: patient compliance and adverse effects.[90] Graham and coworkers[91] demonstrated an overall eradication rate of 87% in a mixed patient group with duodenal ulcer, gastric ulcer and *H. pylori* gastritis who received tetracycline 2000mg plus metronidazole 750mg plus bismuth salicylate (750 to 1200mg of bismuth) daily. However, the most important factor predicting success was patient compliance. When more than 60% of the prescribed medication was taken eradication rates of 96% were achieved; less than 60% resulted in an eradication rate of 69%. Adverse effects, mainly nausea and diarrhoea, are experienced by 7 to 63% of patients receiving triple therapy.[92-94]

These problems prompted several investigators to look for alternative antimicrobial treatment strategies. A concept now emerging is the combination of a proton pump inhibitor with an effective antibiotic. Several studies[95-98] have recently been performed to assess the efficacy of omeprazole plus amoxicillin combinations for eradicating *H. pylori*. The eradication rates reported lie between 38 and 91% and are associated with a lower rate of adverse effects of 2 to 16%. The effectiveness of acid suppression[101-104] plus antibiotic seems promising, and the combination is now entering clinical practice. Further evaluation by direct comparison of different treatment regimens is needed.[94]

Antimicrobial therapy leading to *H. pylori* eradication has been shown to alleviate the host's local immune response in the gastric mucosa, as represented by a decrease in activity (neutrophilic infiltrates) and grade (mononuclear cell infiltrates) of underlying gastritis.[105-107] This is not the case in

persistent *H. pylori* infection after classical acid suppression treatment with H_2-antagonists or proton pump inhibitors.[81,108,109] In fact, an aggravation of gastritis can be found following such therapy.

Lymphoid follicles, a characteristic feature of *H. pylori*–associated gastritis, do seem to persist following antimicrobial eradication therapy, although their number significantly decreases.[110] This suggests a residual state of immune surveillance, allowing an immune response to be mounted in case of reinfection of the host. In low-level persistent *H. pylori* infection associated with chronic atrophic gastritis, eradication may result in replacement of abnormal mucosa by normal healthy mucosa with signs of atrophy no longer being detectable.[111] Although controlled trials are still missing, this observation could have considerable implications for the prevention of gastric cancer in *H. pylori*–positive patients presenting with mucosal atrophy or metaplasia.

2.2 Vaccination

A classic immunological approach to an infectious disease is the development of a vaccine. However, the need for such a vaccine against *H. pylori* is disputed. It can be argued that in time efficient antimicrobial treatment regimens will evolve so that *H. pylori*–infected individuals with ulcer disease can be treated effectively without the necessity to immunise the general population, especially since a large proportion of *H. pylori*–infected individuals remain asymptomatic. However, the association between *H. pylori* infection and gastric carcinoma could make vaccination efficacious. This holds true especially for populations in which there is a high prevalence of the disease and mortality is high, as in third world countries. Studies in Columbia[112] have shown the prevalence of *H. pylori* infection to be 93% in areas of high gastric cancer risk and 68% in low risk areas. The same association has been demonstrated in rural areas in China,[113] where 90% of children become infected by the age of 10 years. Long term infections acquired at an early age may result in chronic atrophy and intestinal metaplasia, followed by the development of gastric cancer.

Although infected individuals mount an intense humoral systemic immune response to *H. pylori* (section 1.3.3), the generation of specific local secretory IgA antibodies against potent conserved antigens of the organism could provide protection following vaccination. These antibodies would prevent adherence of the bacterium to the gastric epithelium and neutralise cytotoxins produced by the pathogen. However, studies concerning vaccine development are still scarce. This may be attributed to 3 factors:

- lack of knowledge as to which immunogens could be used for immunisation against *H. pylori*;
- lack of appropriate animal models, since *H. pylori* is a specific human pathogen that otherwise is found only in primates;
- the poorly characterised cellular immune response towards specific antigens of the organism, since the isolation of antigen-specific T cell clones from gastric mucosa is difficult.[114] Such clones are necessary to identify the antigens that stimulate T cell–mediated responses, thereby providing help to B cells in producing antibodies.

2.2.1 Antigens

Several antigens have been suggested as candidates in vaccine development. Urease[115] is produced by all *H. pylori* strains and is a well-conserved enzyme consisting of 2 subunits with molecular masses of 64 and 30kD. The polar sheathed flagella of *H. pylori* contains unique proteins of 51 and 53kD, and is essential for the bacterial mobility necessary for penetration of the viscous mucous layer.[116] Several adhesins have been characterised from *H. pylori*.[117-119] Antibodies directed against these molecules could prevent bacterial adhesion to the mucosal surface. Possibly the most promising candidates are vacuolating cytotoxin (87kD) and the cytotoxin-associated gene A (Cag A) [128kD]. Cag A is probably the most immunogenic antigen of *H. pylori*: 100% of patients with duodenal ulcers and 60% of patients

with gastric ulcers have serum antibodies against this protein.[120]

2.2.2 Animal Models

A few animal models have been used to study immunisation protocols against *H. pylori*.[121-124] However, most of these studies do not use *H. pylori* but instead use closely related organisms such as *H. mustelae* or *H. felis* in their protocols.

Czinn and Nedrud[122] reported elevated IgA and IgG in serum and mucosal secretions of mice and ferrets following oral immunisation with killed *H. pylori* plus cholera toxin as an adjuvant. Whether or not this response prevents infection could not be tested in this model, since live *H. pylori* does not colonise the stomach of these animals.

Eaton and Krakowka[124] observed in an gnotobiotic piglet model that parenteral immunisation with formalin-killed *H. pylori* was effective in inducing an IgG and IgA response. However, this led to an enhancement of gastritis with increased neutrophilic infiltration and did not protect the animal from bacterial infection. The only study showing a protective effect of oral immunisation was described by Chen and coworkers[123] in an *H. felis* model using specific-pathogen-free mice.

Further research in this area is needed to delineate appropriate models that can be used to test possible vaccines.

3. Conclusion

After the first decade of *H. pylori* research the major significance of this organism in gastroduodenal disease has been established, and many 'non-believers' have converted to 'believers'. Diversity of the individual host's immune response based on inheritance, age or environmental factors could explain the various clinical outcomes of the infection. Antimicrobial therapy will remain a mainstay of treatment, and will become more refined. However, continued research is necessary to characterise further the immunopathogenic principles involved in disease development. Effective therapy for large patient populations can only be developed if these principles are sufficiently understood.

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