Leading article

Vaccine against *Helicobacter pylori*: fact or fiction?

Is there a need?

Antibiotic-based triple therapy is reasonably effective in treating patients with symptomatic *Helicobacter pylori* infection, but this approach is untenable for global control of the infection. In practice, however, anti-*H pylori* therapy is prescribed to an increasing number of patients, in the absence of proven benefit.[1 2] Firstly, anti-*H pylori* treatment is increasingly offered to infected patients with non-ulcer dyspepsia and to asymptomatic carriers. This "test-and-treat" attitude is aimed at controlling the dyspeptic symptoms and at reducing long term risk of gastric malignancies in infected individuals. Secondly, anti-*H pylori* treatment is also advocated as a first approach in *H pylori* positive dyspeptic patients, in an attempt to reduce the overall management costs of these patients, without prior endoscopic documentation of the presence of an ulcer or of other complications of the infection.[3 4] Even though some decision analysis and clinical studies suggest that these different approaches may be beneficial,[3–5] other studies have failed to show potential benefit.[6–8]

The increased prescription of antibiotics for *H pylori* infection has encouraged the emergence of antibiotic resistant strains. Indeed, the efficacy of current therapies rarely exceeds 90%, and strains isolated after treatment failure often show resistance.[9] Resistance to metronidazole is already high in developed countries, and resistance to clarithromycin is increasingly evident. A survey of resistance conducted over five years in Ireland showed that resistance to metronidazole and clarithromycin increased from 32% to 46% and from 5.3% to 8.6%, respectively.[10] Because metronidazole has been available for decades before being used against *H pylori*, this rapid evolution suggests that the selection pressure on *H pylori* developed once antibiotics were prescribed in association with antisecretory agents. If this speculation is correct, the number of patients treated for *H pylori* infection may impact directly on the development of resistance, and accumulated treatment failure may result in the enrichment of the human reservoir with resistant strains. A direct impact on the efficacy of the current treatments may follow[11 12] as evidence suggests that the main reservoir of *H pylori* is the human stomach. Indeed, passage from animals to humans does not seem to be an important mode of transmission, and *H pylori* does not resist well in the environment.

Alternative strategies are therefore needed to control *H pylori* infection. There is ample precedent from experience in the control of other infections to suggest that vaccination may be such an alternative, with the advantage of acting regardless of antibiotic resistance. If, in addition, an anti-*H pylori* vaccine can be used as a treatment, either alone or in conjunction with current treatment, it may help to prevent the emergence of antibiotic resistant strains, preserving the value of antibiotics against this pathogen. Furthermore, if vaccination can prevent and cure *H pylori* infection, its use in populations with high infection rates in childhood would not depend on prior screening. In this regard it should be noted that the long term persistence of the infection implies that even if some public health action is undertaken to prevent further dissemination of *H pylori*, the number of infected people worldwide requiring treatment for peptic ulcer disease alone is beyond the reach of antibiotic based triple therapy. Vaccination is the only approach currently in a clinical stage of development with the potential to lead to global control of *H pylori*.

***H pylori* vaccination: what has been achieved?**

The concept that vaccination was possible came from animal studies which showed that protection against various gastric helicobacter species could be achieved by mucosal immunisation using an antigen and a mucosal adjuvant. The initial studies were performed using whole cell extracts of bacteria and showed that vaccination was possible despite the lack of efficacy of the natural immune defences of the host against infection with *H pylori*.[13 14] However, vaccines based on uncharacterised antigen preparations of *H pylori* are associated with high production costs, difficulties of standardisation, and a high potential for side effects. For these reasons, efforts have been focused primarily on the identification of antigens of *H pylori* able to confer protection. Several protective antigens have been identified, including urease, the cytotoxin VacA, two heat shock proteins (HspA and HspB), and catalase.[15–18] The list of protective antigens is still growing, and the availability in the public domain of the entire *H pylori* genome will certainly facilitate the identification of more vaccine antigens.

Urease is currently the most promising candidate, and its value as a vaccine antigen has been confirmed by numerous studies in mice, ferrets, and non-human primates.[17 19 20] Urease conferred protection against helicobacter infection when delivered either as a native protein or as an enzymatically inactive recombinant protein.[15] In addition, when mice previously infected with *H felis* were immunised with *H pylori* urease, their infection cleared.[21] This therapeutic effect of mucosal immunisation has also been observed in mice immunised with a bacterial lysate of *H felis* and with *H pylori* cytotoxin.[22] Therapeutic immunisation with urease has recently been reported in ferrets naturally infected with *H mustelae*.[19] Infection with *H mustelae* occurs in ferrets soon after weaning, persists for life, induces active chronic gastritis, and is associated with the development of ulceration in a subgroup of infected animals.[23] Thus, therapeutic immunisation is possible in a natural setting of helicobacter infection, confirming that the inability of the natural immune response to clear helicobacter infection can be overcome.

In addition to conferring protection, vaccine antigens should, in theory, have a number of other important characteristics. The antigen should be shared by all *H pylori* isolates without much antigenic variation, and should lack intrinsic toxicity. According to these criteria, the cytotoxin VacA, which is not expressed by all strains and induced erosions when fed to mice, may not be an ideal vaccine candidate.[24] There is also concern about inducing an immune response to HspB because this protein has homologies to the GroEL family of heat shock proteins[16]

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involved in autoimmune reactions.[25] In contrast, urease and HspA are expressed by all *H pylori* strains and do not induce adverse reactions when administered orally with an adjuvant to mice. Urease is also safe when administered to non-human primates.[20]

Immunisation with urease has been studied recently in *H pylori* infected human volunteers. It was found that oral administration of urease alone did not induce systemic adverse reactions and did not modify *H pylori* mediated gastric mucosal inflammation.[26] Urease alone, however, induced no changes in the host immune response to *H pylori* or in the density of bacteria present on the gastric mucosa, underlining the need for an appropriate mucosal adjuvant. More recently, the safety and immunogenicity of recombinant *H pylori* urease was tested when given with a mucosal adjuvant, the heat labile enterotoxin (LT) of *Escherichia coli*. This study confirmed the safety of urease. Urease given with LT induced an immune response and a reduction in the density of gastric *H pylori* infection, an indication that vaccination may lead to cure of human *H pylori* infection.[27]

H pylori vaccination: what remains to be done?

From animal studies, mucosal immunisation resulting in stimulation of the mucosa associated immune system seems to be a prerequisite for protection. The limited human evidence supports this concept, but suggests that the level of stimulation of the immune system obtained in humans with urease plus LT is too low to lead to clearance of the infection.[27] To obtain protective immunity in humans, it is likely that more than one antigen will be required, and that the mode of stimulation of the mucosal immune system will have to be improved.

With regard to the antigen preparation used for immunisation, an association of two or three antigens may elicit a stronger immune response than the use of a single antigen. In mice, a vaccine preparation composed of HspA and the B subunit of urease induced a higher level of protection against *H felis* than either antigen given alone.[16] Similar results were reported with a combination of VacA cytotoxin and urease in *H pylori* infected mice.[28] A combination of antigens may be required both to improve vaccine efficacy and to circumvent possible immunological restriction. This latter phenomenon, recognised recently in mice,[29] may occur in humans and would be prevented by a vaccine made of more than one antigen.

Several other improvements may lead to increased stimulation of the immune response. Firstly, alternate routes of immunisation may be better suited than the oral route to elicit a strong immune response in the stomach. In mice, intranasal or rectal immunisation elicited stronger protection against gastric helicobacter infections than oral immunisation.[30] The importance of the route of immunisation in eliciting mucosal immune responses in various mucosal compartments has already been recognised in humans,[31] but the optimal route to elicit a response strong enough to protect the gastric mucosa has yet to be found. Secondly, the use of detoxified forms of LT may allow the dose of adjuvant used to be increased, with the hope of inducing a more potent immune response. After detoxification, which can be achieved by different genetic interventions on the moiety carrying ADP-ribosyltransferase activity, attenuated LT remained a good adjuvant in mice,[32] and thus is a promising agent for human use. Thirdly, new modes of delivery of the antigen may be used. Recent results in mice indicate that immunisation with genetically engineered bacteria expressing *H pylori* antigens elicits a protective immune response against gastric helicobacter infections.[33] Immunisation with live bacterial vaccines usually requires only one or two doses, does not depend on the addition of extra mucosal adjuvant, and the vaccine can be produced at very low cost. Fourthly, additional improvements to the vaccine should result from a better understanding of the natural immune responses to helicobacter infection and of the mechanisms by which vaccination restores protection. The definition of reliable immunological markers of protection should provide information on the type of stimulation that should be induced by vaccination. Such information is still lacking however.

In conclusion, although *H pylori* infection is now easier to manage on an individual basis, available treatments, which are too expensive and which have been compromised by growing antibiotic resistance, achieve less than satisfactory control of the infection in large populations. A vaccine is a reasonable alternative approach and several steps towards its development have been taken. Despite these accomplishments, much research is still needed before a human vaccine against *H pylori* becomes a reality. Until a vaccine, or any other form of global control of the infection, becomes available, the ability to treat symptomatic patients effectively should be protected. This can only be achieved by using anti-*H pylori* treatment appropriately, by restricting its use to patients likely to benefit directly from cure of the infection.

PIERRE MICHETTI

Division of Gastroenterology,
Room DA-601 – East Campus,
Beth Israel Deaconess Medical Center,
Harvard Medical School,
330 Brookline Avenue,
Boston, MA 02215, USA

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