Clinical review

Helicobacter pylori—More Light, Less Heat

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Several areas of broad agreement exist concerning the management of specific patient groups with clear-cut complications of *H. pylori*-colonization. Other aspects of this infection remain less well defined. These include the mode of transmission and pathogenesis of *H. pylori*, the clinical management of patients who do not have ulcer disease, and the approach to populations at risk of the clinical consequences of this bacterium. This review focuses on the unresolved issues of *H. pylori* infection that are of concern to the clinical gastroenterologist. (Am J Gastroenterol 1998;93:306–310. © 1998 by Am. Coll. of Gastroenterology)

INTRODUCTION

Some 15 years after the start of the modern *Helicobacter* era, after multiple international and national meetings attempting to achieve consensus, and after a steady rise in the number of publications about this bacterium, one might be forgiven for thinking that there is little left to understand about the gastroenterologist's favorite germ. However, as evidenced from some free-flowing discussion at a recent meeting held at Yale University School of Medicine, many of the important issues remain unresolved. We are still in the dark about many aspects of the organism itself, its transmission, how it causes disease, and how we should be clinically managing this infection, both in practice and as a public health issue. The following précis highlights the areas of both knowledge and uncertainty that were explored by a group of *H. pylori* devotees.

EPIDEMIOLOGY AND ANIMAL MODELS

The epidemiology of *H. pylori* has been extensively studied and the risk factors for the acquisition of infection determined. It is clear that most infection occurs in childhood (1) and that infection or reinfection is not a clinical problem for most adults, in developed countries at least (2).

How *H. pylori* is transmitted, however, remains unclear, and it remains possible that more than one route exists (2). The evidence for fecal-oral transmission is based mainly on a small group of children in Africa (3), on contaminated water supplies, and by analogy with hepatitis A (2, 4). Although the organism has been cultured from feces in the developed world, most researchers have only found *H. pylori* in the stool by PCR. Alternative methods of transmission include the oral-oral route, perhaps lurking in dental plaque or by regurgitation of gastric contents, or waterborne—*H. pylori* has been found in the water supply occasionally—not only in Peru, but also recently in Scandinavia, again using PCR (5). Apart from some early attempts by enthusiastic investigators to fulfill Koch's postulates by drinking *H. pylori*, or occasional episodes of epidemic achlorhydria related to sharing common inadequately sterilized endoscopes or gastric tubes, documented transmission from person to person has been largely elusive. Fortunately, the routine use of high level disinfection for endoscopes and reusable biopsy forceps should eliminate iatrogenic transmission of *H. pylori* by gastroenterologists (6).

Perhaps the use of animal models, of which there are many, may clarify the issue of transmission. The earliest animal models required the use of gnotobiotic pigs, but more recently many other animals (cats, ferrets, gerbils, hamsters, rats, and mice) have been infected with a variety of *Helicobacter* species—both nonhuman *Helicobacter* and *H. pylori*. Some of these animals have developed pathology similar to that found in human disease. For example, *H. mustelae* in ferrets produces a multifocal atrophic gastritis. Gastric ulcers can be produced by infection with *H. Heilmanii* (formerly *Gastrospirillum hominis*) in mice (7), or by *H. pylori* in gnotobiotic pigs (8), and some animals even develop MALT lymphoma and cancer. The outcome of infection in certain animal models has been shown to be dependent not only on the bacterium inoculated, but also on the animal's genotype (9). Ultimately, animal models may be useful not only for the development of vaccines, but also to determine the natural history of *Helicobacter* infection.

They may be of utility in the evaluation of the bacterial and host factors that determine clinical outcome and in the elucidation of the mechanism of the association between H. pylori and gastric malignancy.

BACTERIAL PHYSIOLOGY

With the recent publication of H. pylori's entire genome (on paper [1]) and on the internet (at http://www.tigr.org/tdb/mdb/hpdb/hpdb.html), are there any unanswered questions about the bacterium itself? Urease is one of H. pylori's most important enzymes, essential for pathogenicity, a potential immunogen for vaccine development and the basis of many recommended diagnostic tests. This enzyme is located on the external bacterial surface, which is thought to be important in protecting H. pylori as it traverses the acidic gastric lumen to establish colonization. In some interesting recent studies, Phadnis and colleagues noted that in early phase growth in vitro, H. pylori's urease is predominantly cytoplasmic, as it is in other urease-positive bacteria. However, as the bacteria mature, urease becomes expressed on the external bacterial surface. How does this occur? There is no available evidence that secretion of urease occurs. Indeed, specific carriers of the ABC type or the type 3 bacterial transport system that could enable this large protein to move across bacterial cell walls have not been found in H. pylori. Nor does the urease have a signal sequence that would enable trafficking to membranes. Dunn and colleagues postulate that urease ends up on the external surface after H. pylori has undergone an altruistic, suicidal cell lysis, releasing cytoplasmic urease on to other bacteria of the colony (11). Whether or not this occurs, the demonstrable absence of surface bound urease from young bacteria may mean that vaccination with urease as the antigen is unlikely to be successful.

What is the clinical important of the cagA and vacA bacterial genotypes? In general, bacteria possessing the Cag pathogenicity island also express the vacA cytotoxin (with the type s1a signal sequence), but it is clear that H. pylori cannot be neatly divided into virulent and nonvirulent types based on CagA and VacA (12). Approximately half of the world's population is infected by CagA-positive bacteria, yet not all develop clinical sequelae. Other bacterial factors may determine clinical outcome—for example, allelic variations in the recently described ice A bacterial genes, which are expressed after adherence with epithelium, are related to ulcer disease (13).

GASTRIC ACID PHYSIOLOGY

In some infected individuals, particularly those with duodenal ulcer disease, H. pylori alters gastric physiology subtly—somatostatin synthesis is decreased and, consequently, gastrin release is exaggerated (14). In addition, lipopolysaccharide extracts stimulate ECL cell histamine release (15). However, pepsin and gastric acid secretion are not increased in most patients. Despite many small studies over the past few years reporting changes in acid and pepsin

secretion with either the acquisition or eradication of H. pylori, and the fact that acid inhibition is important in current anti-H. pylori therapies, the effect of H. pylori on acid and pepsin secretion remains a subject of considerable debate (16). In patients with duodenal ulcer disease, some studies have shown that eradication of the organism reduces both basal and peak acid output (when followed for long enough), suggesting that H. pylori increases acid secretion. However, it is well described that, in early infection, acid secretion decreases, and at least two acid inhibitory substances have been purified from H. pylori, with one partially sequenced (17). How can the observations that the presence of H. pylori somehow increases the efficacy of omeprazole be interpreted (18)? Is this due to the generation of ammonia by H. pylori with consequent increase of the alkalization of the gastric lumen (19)?

H. PYLORI, LIFE AND DEATH IN THEGASTRIC MUCOSA

Serial biopsies taken over many years from patients infected with H. pylori indicate that the long term consequence of infection may include gastric atrophy and intestinal metaplasia and that, by implication from earlier studies, these may lead to dysplasia and gastric cancer. The recent concerns with regard to the potential for proton pump inhibitors to accelerate this process continues to be debated (20). Although controversial, the concept that decreased acid secretion and gastric atrophy go hand in hand is an old one. Although it was previously held that acid inhibition was the result and not the cause of atrophic gastritis, data from Kuipers et al. have suggested that if infection with H. pylori is present, acid inhibition may result in accelerated atrophy. The mechanism of this effect remains obscure, but pharmacological or surgical reduction of gastric acid secretion are both associated with a more severe inflammatory response to H. pylori, which may lead to more severe epithelial cell damage (21). Interpreting the data remains difficult in part, because of the problems in defining gastric atrophy. The recent publication of the updated Sydney system for the classification and grading of gastritis may be helpful in future studies of atrophy (22). However, whether it will be more clinically useful than its predecessors remains to be seen. It attempts to at least objectively define gastritis using visual analogue scales, and should be lauded for this. However, there is still considerable debate concerning the reversibility of atrophy, whether functional or morphological; most would argue that atrophy is not reversible, but because of potential sampling errors in follow-up biopsy studies, convincing data are lacking. The debates continues.

Many studies have established recently that infection with H. pylori and the secondary mucosal inflammatory response increases gastric epithelial cell proliferation. This may be a necessary step in the process of gastric carcinogenesis, as for many other malignancies. H. pylori probably does not increase proliferation directly; increased cell proliferation is more likely a response to apoptosis (programmed cell death)

induced by the organism or the inflammatory response (23). After a compensatory hyperproliferative response, the balance between apoptosis and proliferation may determine whether ulcers and atrophy develop or, conversely, whether mucosal mass grows in an unrestrained fashion. Again, animal models may be helpful, for example, *H. felis* infection in mice increases cell proliferation, particularly of mucous neck cells, but decreases the number of parietal cells. The hyperproliferative response is more extreme in animals that are hemizygous for p53, suggesting that *H. pylori* may act in concert with other oncogenes and tumor suppressor genes to produce neoplasia. We know little about the effect of *H. pylori* on the normal gastric cell cycle but, interestingly, *Helicobacter*'s lipopolysaccharide displays synergism in gastrin-mediated increased DNA synthesis in ECL cells (15). Because the ECL cell is a crucial link between gastrin and acid in the normal stomach, the interaction of *H. pylori* with this cell may throw light upon some of the discrepant effects of *H. pylori* on gastrin and acid secretion. Whether the ECL cells see *H. pylori*'s lipopolysaccharide directly is doubtful, inasmuch as the ECL cells are not thought to be in communication with the gastric lumen. It is possible that mucosal damage induced by *H. pylori* and disruption of tight junctions may allow access. However, the population of ECL cells does increase in *H. pylori* infection and, in combination with proton pump inhibitors especially, micronodular carcinoids may develop (24).

DIAGNOSIS

Endoscopy cannot be justified merely to diagnose *H. pylori* infection. As a noninvasive test, the urea breath test is extremely useful, particularly in establishing whether active infection exists or whether eradication therapy was successful. The breath test is the only accurate nonendoscopic way to check for successful eradication. Although current practice guidelines may recommend the use of confirmatory breath testing for individuals with complicated ulcer disease, whether confirmatory testing should be performed in uncomplicated cases with continued symptoms is controversial. Testing to confirm eradication in these patient groups as well as in individuals who are asymptomatic after eradication therapy will be driven by cost, accessibility, accuracy, and patient demand in diagnostic certainty. The major drawback of the C^{13} urea breath test is its high cost. It is currently being purposely marketed at a price only slightly below that of endoscopy, and is significantly more expensive in the U.S. than in the rest of the world. However, the newly FDA-approved C^{14} urea breath test is under $100, thus opening the way for market forces to further decrease the costs of breath tests. Nevertheless, if either breath test is to be used as the initial noninvasive diagnostic test, it must surpass the convenience and accuracy of office-based serological tests which, even if not quite as sensitive or specific as laboratory-based serology, are inexpensive, quick, and easy to use. Because there is no gold standard for the diagnosis of *H. pylori*, the choice of diagnostic test will depend more on local resources, experience, and cost-effectiveness rather than on small differences in sensitivity and specificity.

H. PYLORI AND GASTROINTESTINAL DISEASE

How has the situation changed from that in 1994 when the NIH consensus statement declared that all patients with peptic ulcers associated with *H. pylori* should have the organism eradicated, but that more work was needed to evaluate the link between *H. pylori* and nonulcer dyspepsia before treatment would be recommended for these patients? In 1997 the scientific message is basically unchanged, but clinical practice has altered appreciably. Three years ago only die-hard *H. pylori* aficionados commonly used eradication therapy, even for patients with documented ulcer disease. Now primary care physicians are using eradication therapy, for a wide variety of indications, while some practitioners are not even testing for the organism that is to be killed.

It is of interest to reflect on how such a confusing situation has evolved. Of particular concern is whether it will ever be possible to perform the studies necessary to establish cause and effect for nonulcer dyspepsia? Practicing evidence-based medicine while adopting cost-effective approaches to this potential public health problem may even be mutually exclusive. For example, some models suggest that the simplest way to manage a patient with ulcer-like dyspepsia (25), and perhaps even the asymptomatic patient with *H. pylori*, is by *H. pylori*-eradication treatment. Thus, although we still have no hard evidence that *H. pylori* is associated with nonulcer dyspepsia (26), can we ever turn back the clock to a time where a symptom was evaluated carefully in the context of the patient's general health? It is worth asking whether *H. pylori* eradication has permeated the physicians' and the public's mind to such an extent that no one will be happy living with this potential carcinogen in their stomach (27)?

In retrospect, it seems probable that the announcement, in 1994, by the World Health Organization's International Agency for Research on Cancer, that *H. pylori* is a definite carcinogen may have been a little hasty. While accepting the epidemiological association between *H. pylori* and gastric cancer, a recent reappraisal has emphasized the need to keep an open mind on this critical question (28). Is it possible that not all *H. pylori* are bad (29)? The recent increase in the diagnosis of reflux esophagitis and adenocarcinoma of the lower esophagus and gastric cardia has accompanied the natural decline in *H. pylori* infection in the West over the last 50 years. Could these phenomena be related? In general, esophagitis and fundic gastric cancer are not associated with *H. pylori* infection, and in fact, a negative association may exist (30). Indeed, Labenz and coworkers have found that eradicating *H. pylori* from duodenal ulcer patients may even precipitate reflux disease (31).

Currently, conventional wisdom is that *H. pylori* and NSAIDs are independent risk factors in the etiology of ulcers. This may, however, be an oversimplistic interpreta-

tion of studies that have excluded some of the patients most at risk for NSAID ulcers. In addition, some of these reports have relied on relatively insensitive serological assays, the performance of which may be altered by NSAID use (32). A consequence would be an underestimate of the contribution of H. pylori in patients taking NSAIDs, who develop ulcers in many studies in which serology is the sole criterion for the diagnosis of H. pylori infection. In a provocative and potentially important prospective and blinded study, Chan and coworkers found that in patients about to be treated with naproxen, prophylactic H. pylori eradication decreased the risk of ulcers, suggesting that the bacterium and NSAIDs may be synergistic after all (33).

WHOM SHOULD WE BE TREATING?

This is probably the most controversial aspect of H. pylori in 1998. Inasmuch as most are in agreement that a diagnosis of H. pylori infection should not be sought unless treatment is to be undertaken (28), a more pertinent question may be "whom should we be testing?". The only proven benefit of eradicating H. pylori is for patients with ulcers, yet there are a number of arguments, both economic and emotional, but not purely scientific, that in practice dictate that many more patients than just those with ulcers receive treatment. In view of the fact that the ground is moving under our feet continually, it may never be possible to complete the necessary studies to determine whether H. pylori eradication would benefit certain categories of nonulcer patients. For example, the European "Maastricht" consensus meeting held in the fall of 1996 suggested considerably extending the 1994 NIH consensus indications for treatment (34). In addition to all ulcer patients, H. pylori eradication was recommended, not surprisingly, for early MALT lymphomas (preferably in expert centers, in the context of clinical trials) and also for all patients who had undergone gastrectomy, whether for cancer or ulcers. The argument for treating cancer patients was the persuasive study of a fairly small group of Japanese patients who had an early mucosal gastric cancer resected (35). Those who thereafter had H. pylori eradicated exhibited a reduced chance of a second cancer.

Are we to recommend treatment based on a single report? In addition to these "definite" indications for treatment, the European experts also considered other types of patients in whom H. pylori eradication therapy may be desirable. These included patients with non-ulcer dyspepsia, those with severe (defined macro- or microscopically) gastritis, with intestinal metaplasia type II and III, dysplasia, and even atrophy (although we really have no evidence that any of these early precancerous lesions will regress). Furthermore, the European consensus felt that there was probably a need to treat patients who were receiving maintenance proton pump inhibitors (at variance with the recent conclusions by the FDA), patients with a family history of gastric cancer, patients taking or about to take NSAIDs, and finally, all patients who desire treatment. And, in 1998, what patient

would not choose to eradicate the organism that is so vilified in the popular press? Agonizing about whether particular groups of patients ought to have Helicobacter eradicated may be a purely academic exercise, because the desires of patients may be a prime consideration as to whether they are treated—or will they be? In the age of managed care, the final and perhaps noisiest arguments about who receives therapy may not come from clinicians or patients, but from those who hold the pursestrings.

H. PYLORI AND THE COMPUTER

In the last few years, an increasing number of analyses have been performed, aimed at determining the cost and benefit of a variety of different managements for the H. pylori-infected patient. Almost all have modeled best available estimates to a theoretical population, few have "closed the loop" by reapplying the recommended approach to a real population. All agree that, for peptic ulcers associated with H. pylori, eradication therapy is not only the most clinically efficacious but also the most cost-effective long term treatment. It is, however, still unclear what to do with patients with dyspepsia in whom we do not have a definitive diagnosis. Should they be screened for H. pylori and treated according to the H. pylori result (either with or without an endoscopy), or be treated blindly with anti-H. pylori medications and/or antisecretory therapy? Alternatively, would it be cost-effective to test and simply eradicate H. pylori from all, including the asymptomatic? Even as algorithms are being developed and used—for example, suggesting referring to gastroenterologists for endoscopy only those patients who may have a malignancy or who fail "conventional" treatment (36)—the pressure is on primary care physicians to "test and treat" for all patients. For example, one recent analysis concluded that the "treat patients and see" approach will always be less expensive than doing endoscopy in H. pylori-positive patients, unless endoscopy costs can be reduced by 90% or more (37). However, these models are only as good as the data on which they are based. Can we be sure that someone who has had H. pylori eradicated for ulcer disease will never have ulcers or ulcer-like symptoms again? H. pylori-negative duodenal ulcers do exist (38, 39) and, rather than being a great rarity, they may comprise around a quarter of all duodenal ulcers in U.S. populations (Duane Webb, data presented at Digestive Diseases Week, Washington, D.C., May 1997). Further unknowns complicate our models. For example, is it really of no consequence to miss the occasional gastric cancer? How predictable and how expensive to society is the emergence of non-Helicobacter bacterial resistance secondary to the indiscriminate use of antibiotics?

There are persuasive arguments that the eradication of H. pylori should be viewed as a public health measure to prevent future gastric cancer. Again, evidence from the computer suggests that screening for H. pylori in the middle-aged population and eradicating H. pylori from those

who test positive could be relatively cost-effective; no more expensive than other cancer prevention strategies, if eradication reduces the gastric cancer risk by more than 20% (40). However, it may be unrealistic to expect that eradicating H. pylori from the middle-aged will reduce the gastric cancer risk at all (there is no good evidence that gastric preneoplasia is reversible); prospective randomized trials of large numbers of patients followed for many years will be necessary to answer this important question. It may be that intervening in the case of children is the only way to prevent the long term impact of infection.

Finally, as noted by Howard Spiro in his eloquent summary at the end of the conference, are we falling into the trap of blaming H. pylori for all our ills? The idea of an alien invading and living in our stomachs and causing disease may be popular for those who would like to blame unhappiness and pain on an external agent. In scapegoating this bacterium and closing our minds to other possibilities, we may be fooling ourselves and our patients. We should remember that a long term obsession with acid previously soured our judgment, and we should be cognizent of the potential relevance of pepsin and the possibility of inherent mucosal defects in the genesis of esophago-gastro-duodenal mucosal disease.

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