0002-9270/88/8305-0479
THE AMERICAN JOURNAL OF GASTROENTEROLOGY

Vol. 83, No. 5, 1988
Printed in U.S.A.

Controversies, dilemmas, and dialogues

This section is dedicated to a candid discussion of present clinical problems. The section editors have selected both the topics and the authors, who are considered prominent authorities on the subjects.

Section Editors: Lawrence Brandt, M.D., F.A.C.G., and Arvey Rogers, M.D., F.A.C.G.

Should We Now, Routinely, Be Examining Gastric Biopsies for *Campylobacter pylori*?

GASTRIC MUCOSAL BIOPSY: AN ESSENTIAL INVESTIGATION IN PATIENTS WITH DYSPEPSIA

Barry J. Marshall, MB.BS., F.R.A.C.P.

Department of Internal Medicine,
Division of Gastroenterology,
University of Virginia, Charlottesville, Virginia

INTRODUCTION

The recent rediscovery of *Campylobacter pylori* has fired renewed interest in gastritis as a cause of dyspepsia, and as the lesion responsible for the "ulcer diathesis." In duodenal ulcer, the prevalence of this type of type B gastritis approaches 100% (1, 2). Gastritis heals once *C. pylori* has been eradicated (2, 3) but a definite link between histological gastritis and symptoms has not been proved or disproved. When contemplating a diagnosis of *C. pylori*, therefore, the gastroenterologist needs to know who to test for the bacterium, the meaning of a positive result, and when to treat.

WHO HAS *C. PYLORI*?

The hallmark of many successful pathogens is an asymptomatic but equally infectious carrier state. Although apparently healthy adults can have gastritis due to *C. pylori*, this *C. pylori* "carrier state" is largely irrelevant to the clinician, because among the cases of *C. pylori* he sees most will be patients with dyspepsia, rather than asymptomatic persons. In endoscopy populations, most of the ulcer patients and about half of those without ulcer will have *C. pylori*-associated gastritis (4).

"Moynihan's disease," as described by Spiro (5), exactly fits our current understanding of *C. pylori*-associated gastritis. Moynihan believed inflammation of the gastroduodenal mucosa functioned as the "soil" upon which ulcerative processes acted. If so, then patients with gastroduodenal inflammation (many microscopic mucosal defects) did not require a macroscopic ulcer crater for acid to enter the mucosa and cause pain.

Patients with gastritis but without visible ulcer craters may have large areas of abnormal mucosa with mucus depletion of the epithelial cells, and microscopic abscesses (2). A heavy cellular infiltrate in the mucosa may have subtle effects on motility of the gastroduodenal segment, which could explain vague symptoms such as "gas," "bloating," and nausea seen both in patients with duodenal ulcer and the nonulcer dyspepsia syndrome. *C. pylori* hydrolyzes urea with its urease enzyme. The ammonia so produced may be toxic, and CO_2 generated could contribute to "gas" symptoms.

The gastroenterologist who understands the concept of Moynihan's disease performs endoscopy not just to search for ulcer craters, but also to assess the integrity of the gastroduodenal mucosa. If an ulcer is visible, a biopsy may be take to exclude malignancy in the lesion, but separate mucosal biopsies are also taken to exclude a more generalized mucosal defect.

Even if the stomach and duodenum appears completely normal, the gastroenterologist should still take mucosal biopsies. Thus, patients with a generalized abnormality of the gastroduodenal mucosa may be separated from those with completely normal stomachs.

Received Jan. 12, 1988; accepted Jan. 18, 1988.

DIAGNOSIS OF *C. PYLORI*

Biopsies to assess for *C. pylori* and gastritis should be taken from intact mucosa, avoiding the lesser curve which may be affected by intestinal metaplasia. The specimens should be fixed in formalin, stained with both hematoxylin and eosin and Giemsa stain, and examined under oil for curved bacteria.

With a sensitivity approaching that of histology, the biopsy urease test (6) is the most rapid way to diagnose *C. pylori*. It has the advantage of producing a result in the endoscopy room, allowing immediate diagnosis and treatment. As virtually all persons with *C. pylori* have gastritis, a presumptive diagnosis of gastritis can be made whenever the bacterium is detected.

Other diagnostic methods have less practical application at present. Gram stain of tissue is time consuming, and culture misses *C. pylori* in patients who happen to take medications that inhibit the bacterium. The urea breath tests are available in only a few centers (7, 8) but enable noninvasive follow-up of *C. pylori* after treatment, when endoscopy is not thought necessary. Serology is useful to screen patients for *C. pylori* infection.

WHO SHOULD YOU BIOPSY?

All patients should be biopsied. There is no way you can tell which patients have severe gastritis by merely looking at the mucosa (9). Biopsies for *C. pylori* will only prolong the endoscopy by 3–5 min because they do not have to be carefully aimed like biopsies of ulcer borders. In elective endoscopy patients without known coagulopathy, gastric mucosal biopsy has a negligible risk. At the University of Virginia, endoscopy patients usually have one sample taken for urease test and two samples for histological examination.

Patients who are happy taking current remedies, such as H_2 receptor antagonist therapy, need not be treated for *C. pylori*. If their disease worsens, the knowledge that *C. pylori* is present will give a useful future therapeutic option. *C. pylori* may be difficult to eradicate, so the physician should not usually embark on therapy unless he is prepared to carry it through and confirm bacteriological cure. Such a course may not be justified in well patients.

Some patients respond poorly to conventional ulcer therapy because it is expensive and may thus be taken only during severe symptomatic relapses. In these patients a trial of an antibacterial regimen, even if follow-up is unlikely, may be justified.

When ulcer disease is associated with ingestion of nonsteroidal anti-inflammatory drugs (NSAIDs) an antral biopsy will be normal if NSAID is the sole cause of the ulcer. These patients will do well if taken off the NSAID. When *C. pylori* is present, however, a diffuse mucosal lesion exists, and the ulcer may be unrelated to the NSAID. In these patients, it may be possible to continue NSAID if the *C. pylori*-associated gastritis is healed.

Surgical procedures should never be performed in ulcer patients before diagnosis and treatment of *C. pylori* has been considered. This option should be discussed with the patient before referral to a surgeon. It is my experience that even patients with pyloric stenosis will do well on antibiotics if *C. pylori* is implicated.

Some postsurgical syndromes may be related to persisting *C. pylori* infection. Before referring a patient for further surgical treatment of "bile reflux gastritis" or "stomal ulcer," perform multiple gastric biopsies to exclude *C. pylori*. Bile reflux may make the bacteria difficult to find, so at least four biopsies should be taken for histology.

WHAT TREATMENT?

At the present time, treatment will be a 21-day course of bismuth subsalicylate (Pepto-Bismol), 30 ml, or 2 tabs qid on an empty stomach. Supplemented with either 2 g amoxycillin daily on days 7–21, 2 g erythromycin daily on days 7–21, or 1.5 g metronidazole daily on days 10–20. Each of these therapies has a bacteriological cure rate of about 50% (10).

CONCLUSION

Therapy for *C. pylori* is controversial, and will remain so until prospective double-blind studies have proven its benefit. In practical terms, however, what else have we got to offer patients with gastritis and severe recurrent ulcer disease? At present, the only curative ulcer therapy is surgery, whereas medical therapy is palliative and expensive.

If *C. pylori* gastritis was rare and was always a mild disease, we would be content to wait for the major research centers to complete their prospective double-blind studies. Instead, we see very sick patients with *C. pylori*, and the disease appears to be extremely common. In this circumstance, the gastroenterologist should routinely look for the bacterium in all dyspeptic patients, form his own opinion about disease associations, and weigh the possible benefits of antibacterial treatment against the expectations of current therapy.

Reprint requests: Dr. Barry J. Marshall, Department of Internal Medicine, Division of Gastroenterology, Box 145, University of Virginia, Charlottesville, VA 22908.

REFERENCES

1. Hui WM, Lam SK, Chau PY, et al. Persistence of *Campylobacter pyloridis* despite healing of duodenal ulcer and improvement of

accompanying duodenitis and gastritis. Dig Dis Sci 1987; 32:1255–60.
2. Rauws EAJ, Langenberg W, Houthoff HJ, et al. *Campylobacter pyloridis*-associated chronic active antral gastritis: A prospective study of its prevalence and the effects of antibacterial and antiulcer treatment. Gastroenterology 1988;94:229–38.
3. McNulty CA, Gearty JC, Crump B, et al. *Campylobacter pyloridis* and associated gastritis: Investigator-blind, placebo-controlled trial of bismuth salicylate and erythromycin ethylsuccinate. Br Med J [Clin Res] 1986;293:645–9.
4. Marshall BJ, Warren JR. Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. Lancet 1984;1:1311–5.
5. Spiro HM. Moynihan's disease? The diagnosis of duodenal ulcer. N Engl J Med 1974;291:567–9.
6. Marshall BJ, Warren JR, Francis GJ, et al. Rapid urease test in the management of *Campylobacter pyloridis*-associated gastritis. Am J Gastroenterol 1987;82:200–10.
7. Marshall BJ, Surveyor I. Carbon-14-urea breath test for the diagnosis of *Campylobacter pylori*-associated gastritis. J Nucl Med 1988;29:11–6.
8. Graham DY, Klein PD, Evans DJ Jr, et al. *Campylobacter pylori* detected noninvasively by the ^{13}C-urea breath test. Lancet 1987; 1:1174-7.
9. Goldner, FH, Boyce W. Relationship to bile in the stomach to gastritis. Gastrointest Endosc 1976;22:197–9.
10. Goodwin, CS, Marshall BJ, Blincow, ED, et al. Prevention of nitroimidazole resistance in *Campylobacter pylori* by co-administration of colloidal bismuth subcitrate: Clinical and in vitro studies. J Clin Pathol 1988 (in press).

SHOULD I SEARCH FOR *CAMPYLOBACTER PYLORI* IN MY PATIENTS? MUCH ADO ABOUT NOT MUCH?

David Y. Graham, M.D., and Patrice A. Michaletz, M.D.

Digestive Disease Section, VA Medical Center, and Baylor College of Medicine, Houston, Texas

INTRODUCTION

The current popularity of *Campylobacter pylori* as a putitive cause of disease (*e.g.*, peptic ulcer or nonulcer dyspepsia) has prompted many physicians to ask, "Should I try to identify whether this organism is present in my patients?" or "Should I treat my patients for *C. pylori* infection?" At the present time, we believe that the answer to both of these questions is *NO* and we will use this short "position paper" to defend those recommendations.

C. PYLORI INFECTION

There is not much information available concerning the early phase of *C. pylori* infections, but available evidence suggests that acute *C. pylori* infection is associated with nausea, epigastric pain, and vomiting (1–4). Although symptoms with the acute attack may be clinically severe, they resolve within 2 wk (usually within 5–7 days).

At the time symptoms appear (or slightly before), there may be increased basal acid secretion which is soon followed by hypochlorhydria or achlorhydria; several months may be required before acid secretion returns to normal (2, 5, 6).

C. pylori is now accepted as a cause of superficial (primarily antral) gastritis (1, 7, 8, 9). Histologically, acute *C. pylori* infection is associated with an intense superficial gastritis characterized by polymorphonuclear leukocyte infiltration. If the infection continues, the histological picture gradually changes to a milder gastritis in which the infiltrate contains both acute and chronic inflammatory cells (2, 7). Whether clinically mild and self-limited infections occur is unknown, but reports of two cases suggest that they do (3, 4). Whether the *C. pylori* infection ultimately spreads to involve the entire stomach leading to chronic atrophic gastritis remains unknown; there are no real data to confirm or deny that possibility.

C. pylori as the cause of peptic ulcer

C. pylori is not *the cause* of peptic ulcer disease. This statement is supported by the following: *1*) Asymptomatic *C. pylori* infection is extremely common (much more common than peptic ulcer); for example, *C. pylori* infection is present in more than 80% of patients over the age of 60 (9, 10). *2*) Not all patients with peptic ulcer have *C. pylori* infection. *3*) Duodenal ulcer disease patients with *C. pylori* infection can be "cured" of ulcer by highly selective vagotomy while the *C. pylori* infection continues unabated (11). We do not mean to imply that *C. pylori* infection may not be a major contributory factor in the pathogenesis of peptic ulcer disease but, instead, emphasize that the relationship of *C. pylori* to ulcer disease must be much more complicated than some would suggest.

There are a number of therapies that will accelerate healing of peptic ulcers; thus, the presence of *C. pylori* gastritis in conjunction with ulcer disease has little influence on current patient management. If *C. pylori* becomes clearly established as an important factor influencing the rate of ulcer recurrence (it has already been shown not to influence ulcer healing rates) or predisposition toward ulcer, we may, in the future, be required to adjust our approach to ulcer therapy. Meanwhile, we may remain content with the knowledge that our ulcer patients are receiving optimal treatment.

C. pylori and nonulcer dyspepsia

The patient with nonulcer dyspepsia (epigastric pain, in whom no macroscopic pathology is found in the esophagus, stomach, duodenum, or biliary tract) rep-

Received Aug. 13, 1987; accepted Jan. 18, 1988.