Campylobacter pylori infection: diagnosis and therapy

This issue of the Journal contains two useful articles on the subject of *Campylobacter pylori* infection. The first, by Borody et al. from Sydney (page 431), evaluates a bismuth–antibiotic regimen for the treatment of *C. pylori*-associated gastritis and peptic ulcer disease. The second article, by Surveyor et al. from Perth (page 435), describes a rapid breath-test for the diagnosis of gastric *C. pylori* infection, and compares this new test with commonly used invasive (endoscopic biopsy and culture) and non-invasive (serological) methods of diagnosis.

Taking first the issue of the diagnosis of *C. pylori* infection, one should pose the question: "Who has *C. pylori* infection?". Serological studies have shown that 20% of all Australian adults are infected with *C. pylori*.[1] The prevalence is age-related so that, in middle-aged persons, about 40% of Australian adults are infected[2] whereas in young persons the infection rate is only 5%–10%.[2] In some ethnic groups, infection is far more common, particularly in Vietnamese, Chinese and, to a lesser extent, Mediterranean races.[3]

At any point in time most persons with *C. pylori* infection are asymptomatic, perhaps representing a "carrier state" in which the only manifestation of the disease is histological gastritis. However, these "carriers" of *C. pylori* are investigated for upper gastrointestinal symptoms about twice as often as are persons without *C. pylori* infection,[1] and are far more likely to develop overt peptic ulcer disease.

In patients who undergo investigation for suspected peptic ulcer disease, *C. pylori* infection is found commonly. The organism is present in 80% of all patients with proved ulcer craters.[4] It also is found in 50%–60% of patients who suffer indigestion without an ulcer: so-called non-ulcer dyspepsia.[4] Thus, of all Australian patients with chronic upper gastrointestinal symptoms, at least half have *C. pylori* infection and gastritis.

There appears to be no characteristic clinical syndrome (apart from known peptic ulcer disease) which enables the clinical diagnosis of *C. pylori* infection. Therefore, diagnostic tests must be used to exclude the diagnosis of *C. pylori* infection in persons with chronic upper gastrointestinal symptoms.

Serological tests for the presence of *C. pylori* infection have been available at a few centres since 1985.[5] As patients usually present in the chronic stage of the infection, specific immunoglobulin G is present typically in a high titre. Therefore, serological tests are useful to screen for the presence of *C. pylori* infection in patients with dyspepsia. A positive test-result means that the patient has continuing *C. pylori*-associated gastritis, or has been infected recently with *C. pylori*. As pointed out in the article by Surveyor et al., antibodies to *C. pylori* may persist for months or years after the organism's accidental or deliberate eradication, so antibody tests are unsuitable to confirm bacteriological cure of the infection.

However, a negative serological test-result is useful because patients with such results who are not taking non-steroidal anti-inflammatory drugs are very unlikely to have peptic ulcer disease. In the article by Surveyor et al., the described serological test gave positive results in all but one patient with *C. pylori* infection (sensitivity, 97%), but it produced many false-positive results. This may have been because some of the patients with negative results for the presence of *C. pylori* infection had been treated effectively for *C. pylori* infection in the past with bismuth products and/or antibiotic agents. These "false-positive" serological test-results emphasize the need for a more specific test to confirm the diagnosis of *C. pylori* infection, particularly after therapy.

The ^{14}C urea breath-test that is described by Surveyor et al. detects the presence of urease enzyme as produced by *C. pylori* organisms in the gastric mucus. As urease cannot be produced by mammalian cells, it is a marker for bacterial colonization of the stomach, that is, by *C. pylori*. As soon as the isotopic urea comes in contact with the gastric mucosa it is broken down to form carbon dioxide and ammonia. This carbon dioxide, which contains the labelled carbon isotope, is expired in the breath. As the total radiation dose to marrow or gonads is only marginally above the background level (less than 10^{-5} Sv per test),[6] the test is suitable for repeated use except in pregnant women. Because the breath-test detects actual live (urease-producing) *C. pylori* organisms, it is able to confirm a cure of *C. pylori* infection if it is performed one month after antibacterial therapy is ceased.

When non-invasive methods for the diagnosis of *C. pylori* infection become available more generally, any medical practitioner will be able to diagnose *C. pylori* infection and to determine the results of antibacterial therapy. The combination of serological tests and a breath-test offers a sensitivity and specificity that are exceeded only by the examination of multiple gastric-biopsy samples by culture and histological methods.

There always will be patients in whom endoscopy is necessary and, in this group, biopsy methods of diagnosis will be more cost-effective. Screening for the presence of *C. pylori* infection may be performed rapidly in the endoscopy room with a "CLOtest" rapid urease test.[7] Culture of *C. pylori* may permit the antimicrobial sensitivity testing of *C. pylori* and a better selection of antibacterial therapy. Histological examination will provide information as to the severity of the mucosal damage that is associated with *C. pylori* infection, but presently it is of doubtful practical use in the management of patients. However, even in novice laboratories, *C. pylori* infection can be diagnosed accurately or excluded on the basis of the examination of at least two adequate gastric-mucosa biopsy specimens when these are stained with a simple Giemsa stain. In contrast, few microbiology laboratories would be able to detect the presence of *C. pylori* infection in 100% of patients as cited by Surveyor et al. Usually, a microbiological sensitivity of only 80%–90% will be obtained.[8]

The diagnosis of *C. pylori* infection is irrelevant if there is no intention of treating the patient. The risks of therapy apply mainly to persons in whom *C. pylori* infection exists asymptomatically in the presence of symptoms that are caused by a second, more obscure, diagnosis. The benefits of therapy apply especially to persons in whom *C. pylori* infection is a major predisposing factor for recurrent duodenal ulcers. Clinically and histologically, patients with *C. pylori* infection in whom endoscopy produces a normal result often are indistinguishable from patients with peptic ulcer disease; this suggests that *C. pylori* infection produces a clinical spectrum that ranges from asymptomatic gastritis, through non-ulcer dyspepsia, to overt ulceration. The question of whom to treat will be answered only when double-blind studies to evaluate effective therapies for *C. pylori* infection are published.

In an attempt to provide such an effective therapy for *C. pylori* infection, Borody et al. evaluated a regimen that comprised colloidal bismuth subcitrate (108 mg, four times a day for four weeks), tetracycline (500 mg, four times a day for four weeks) and metronidazole (200 mg, four times a day for 10 days). For all patients in the study the presence of *C. pylori* infection was proved by biopsy examination; half the patients had associated histological gastritis with non-ulcer dyspepsia and the remaining patients were known to have duodenal ulcer disease. Active ulcer craters were treated with H_2-receptor antagonist agents before triple therapy was commenced. This produced a consistent "well" (no-ulcer) baseline state for all patients but, in retrospect, may not have been necessary since colloidal bismuth subcitrate is a recognized ulcer-healing agent and full therapeutic doses of the drug were taken for one month.

Significant side-effects that necessitated a change of therapy occurred in fewer than 10% of patients, the most severe being colitis that was caused by infection with *Clostridium difficile* in one patient. Follow-up biopsy samples were taken one month after the 100 patients completed treatment. Other studies have shown that negative results of the examination of biopsy samples one month after therapy

for *C. pylori* infection can predict a long-term bacteriological cure.[9] In this study, eradication of *C. pylori* infection was achieved in a remarkable 94% of patients. Although there was no control group of untreated patients, the spontaneous disappearance of *C. pylori* infection is known to be very rare, so the triple therapy must have been responsible for its eradication.

Long-term follow-up in 64 patients who were studied for 12 to 37 months (mean, 19.3 months) after treatment for *C. pylori* infection revealed a reinfection rate of only 6%; the same low rate was found in smaller Dutch[10] and Australian[9] studies. Thus, when *C. pylori* infection is treated effectively, reinfection is rare.

Finally, Borody et al. attempted to evaluate the effect of such therapy on duodenal ulcer disease in 92 patients who were reviewed at nine to 37 months after treatment for *C. pylori* infection. None of the patients was taking H_2-receptor antagonist agents regularly, although presumably some patients were taking these medications intermittently. Recurrences of duodenal ulcers were found only in patients with recurrent *C. pylori* infection.

As the authors admit, double-blind data would be more convincing than are data from an open study. On the other hand, the natural history of a duodenal ulcer in Australia is one of rapid relapse after the cessation of H_2-receptor antagonist therapy. In most published studies, a relapse rate of more than 75% has been seen in the first six months after the healing of an ulcer.[9] Even in patients with mild ulcer disease, a relapse rate of less than 20% would be incredible.

Borody et al.'s data are consistent with those from double-blind studies that have been reported from Ireland[11] and Western Australia,[9] in which patients in whom *C. pylori* infection was eradicated usually were cured of their duodenal ulcer disease. In these double-blind studies, patients underwent endoscopy more often and, in some patients, relapse was determined on clinical grounds without the presence of an actual ulcer crater.[9,11] In spite of this, the proportion of patients who required a continuation of therapy was only 20% compared with more than 85% of patients in the control group who were treated with cimetidine. A consistent finding in Borody et al.'s and other studies[9,11] is that continued smoking has no deleterious effect on duodenal ulcers after *C. pylori* infection has been eradicated.

Assessed convervatively, Borody et al.'s unblinded data indicate that triple therapy is relatively safe, and that it eradicates *C. pylori* infection in more than 80% of patients. Reinfections occur in fewer than 10% of patients who are followed-up for one year. After the eradication of *C. pylori* infection, the recurrence of a duodenal ulcer is rare, most patients require no further acid-reducing therapy and maintenance therapy is not warranted.

As stated above, the acceptance of *C. pylori* infection as a major causative factor in cases of duodenal ulcer, gastric ulcer, non-ulcer dyspepsia and gastric cancer will depend on the results of double-blind studies in Australia and overseas. Methods for the diagnosis of *C. pylori* infection soon will be available to most clinicians, and treatment is readily available with well-known drugs.

My own practice is to perform a diagnostic screening test for the presence of *C. pylori* infection in all patients with dyspepsia and to offer antibacterial therapy as a therapeutic option. After the eradication of *C. pylori* infection, antacid medication and H_2-receptor antagonist agents are reduced at the discretion of the patient. In uncomplicated ulcer disease and non-ulcer dyspepsia, I cease all therapy after the eradication of *C. pylori* infection. In patients with complicated ulcer disease or previously silent bleeding ulcers, I repeat endoscopy three months after the cessation of all therapy.

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Diabetes data — into the nineties

Two articles in this issue of the Journal deal with opposite ends of the diabetes spectrum: one, by Hamblin et al. (page 439), presents inhospital mortality data that are related to acute complications; and the other, by King et al. (page 444), presents data from a community-based survey. Both raise issues of public-health and epidemiological importance.

Hamblin et al. present a clinical audit of cases of ketoacidosis and hyperosmolar coma from the Alfred Hospital in Melbourne. This is the latest chapter in the documentation — which now spans three decades — of this centre's experience in the management of these complications. We are reminded of the need for scrupulous attention to detail. Granted that, modern treatment methods should ensure that such excellent results are attainable Australia-wide. It is of note that among the patients with hyperosmolar coma, eight of the 12 deaths occurred in patients who had not been identified as suffering from diabetes previously. The authors conclude that our main chance to improve the outcome in relation to these complications will not be found in hospital, but rather in the prevention of their occurrence by the earlier identification of diabetes.

How can diabetes be identified earlier? For now the answer lies in educating the public and in raising the public profile of diabetes. An example of a novel approach to this is the initiative of the Victorian Government to use the funds that are raised by the excise on tobacco for the establishment of a Victorian Health Promotion Foundation. This body, *inter alia*, has made money available to organizations such as Diabetes Australia to sponsor sporting and cultural events and to buy the advertising space that the tobacco industry has been obliged to vacate. It is pleasing to see that the WA Government, with the encouragement of the Australian Medical Association, looks set to follow suit.

How else can diabetes be identified? Should we screen communities for the presence of diabetes? This issue was addressed in the Journal in 1985.[1,2] Outside research studies, and pending the results of trials of the early detection of non-insulin-dependent diabetes mellitus and of interventions which now are in progress, the answer to this question remains "no" at present.[3]

The community-based study by King et al. is a descriptive report from the Tasmanian Insulin-treated Diabetes Register. One striking finding is that more than 90% of insulin-treated diabetic patients were hospitalized at the time of diagnosis. This may surprise diabetologists elsewhere in Australia but, at present, Tasmania is unique in having defined this statistic and in being in a position to discover if this number could be reduced in the future. Certainly the opportunity appears to be ripe to make greater use of outpatient management.

For the rest of Australia, these issues remain in the realm of speculation, anecdote or extrapolation. Also of note is that the majority of Tasmanian diabetic patients who take insulin monitor their own blood-glucose levels. Again, in Tasmania's "North Island" we are ignorant on this point, but if this pattern were typical of that in the