Does treatment of Helicobacter pylori with antibiotics alone heal duodenal ulcer? A randomised double blind placebo controlled study

S-K Lam, C-K Ching, K-C Lai, B C Y Wong, C-L Lai, C-K Chan, L Ong

Abstract

Background—Treatment of Helicobacter pylori infection prevents duodenal ulcer relapse. It has not been established if treatment of the infection heals duodenal ulcer.

Aim—To test the hypothesis that treatment of the infection was associated with healing of duodenal ulcer.

Methods—A randomised, double blind placebo controlled trial was performed to study the efficacy of an antibiotic only regimen consisting of 300 mg metronidazole, 500 mg amoxycillin, and 250 mg clarithromycin, each given four times daily for two weeks, in the healing of duodenal ulcer as assessed by endoscopy. Symptoms were controlled with acetylsalicylic acid and antacids.

Results—Of 100 consecutive patients with endoscopically established duodenal ulcer, 97 with positive rapid urease test on antral biopsy specimens were admitted into the study and 81 completed the trial. Of these, 40 were randomised to receive antibiotics and 41 to receive placebo. Treatment with antibiotics resulted in 92-5% (95% confidence interval 84-3-100) healing at four weeks and 100% at eight and 12 weeks; the corresponding healing rates for placebo treatment were respectively, 36-6%, 61%, and 63-4% (95% CIs 21-8-51-3, 46-0-75-9, and 48-7-78-2 respectively). The differences between the two treatment groups were significant at p<0-001 at each time point and by life table analysis. Clearance of H pylori as assessed by urease test on antral biopsy specimens at four weeks and eradication of the organism as determined by 13C-urea breath test at eight weeks were achieved in 85% and 62-5% of patients respectively. Duodenal ulcer healed at four weeks in 87-2% and 86-2% (95% CIs 76-7-97-7 and 73-7-98-8) of patients in whom H pylori clearance or eradication, was achieved, versus 42-9% and 51-9% (95% CIs 27-9-57-8 and 38-3-65-5; p<0-001 and <0-003 respectively) in whom these processes failed. Stepwise discriminant analysis on 32 clinical, personal, and endoscopic characteristics as well as H pylori clearance and eradication identified H pylori clearance as the most discriminative variable for the healing of duodenal ulcer at four weeks, followed by ulcer depth and eradication of the organism.

Conclusions—Treatment with an antibiotic only regimen was effective for the healing of duodenal ulcer, and clearance as well as eradication of H pylori contributed significantly to the healing. The results constituted the strongest evidence to date that H pylori infection was aetiologically related to duodenal ulceration, and support the concept of treating duodenal ulcer associated with H pylori as an infection and relieving its symptoms with acid reducing agents such as antacids.

(Result) Gut 1997; 41:43-48

Keywords: Helicobacter pylori; antibiotics; eradication; duodenal ulcer; factors affecting healing

The finding that treatment of Helicobacter pylori infection of the stomach prevents the relapse of duodenal ulcer1-3 forms the first clue that the organism has an aetiological role in this condition. The recognition that placebos heal about one third of duodenal ulcers1 and that they do so in the presence of H pylori infection2 seems, however, to be against such a role. Furthermore, because the therapeutic regimens used today for the treatment of the infection and for ulcer healing invariably contain, in addition to antibiotics, agents such as colloidal bismuth subcitrate, proton pump inhibitors, or sucralfate, which have established ulcer healing efficacy as well as a suppressive action on H pylori infection,4-8 it remains unknown if treatment of the infection itself heals duodenal ulcer. Such information has important implications in the aetiology and treatment of this condition. We report the first randomised, double blind placebo controlled study on the efficacy of an antibiotic regimen directed against H pylori infection, consisting of metronidazole, amoxycillin, and clarithromycin—but not including any known ulcer healing agent—in the short term healing of duodenal ulcer.

Methods

Patients

Patients aged between 18 and 79 years were recruited from those attending the medical outpatient clinics and those admitted to the general medical wards of the University Department of Medicine, Queen Mary Hospital, Hong Kong. They were excluded from consideration if they had a concomitant medical problem, particularly renal diseases, cardiovascular diseases, diabetes mellitus, or chronic
obstructive airways diseases, pyloric stenosis, previous gastric operations for ulcer, or an associated gastric ulcer, or if they had been treated in the previous six weeks with any antibiotic or known antiulcer agent including H2 antagonists, proton pump inhibitors, colloidal bismuth subcitrate, and sucralfate. Patients were interviewed by research nurses in relation to their ulcer and related symptoms according to a detailed questionnaire, and their clinical and personal characteristics as listed in Table 1 were recorded as previously described.

ENDOSCOPY

Endoscopy was performed with a forward viewing videoscope (Olympus, Tokyo or Pentax, Tokyo). Patients were recruited if they had an endoscopically demonstrated duodenal ulcer with the largest diameter measuring 5 mm or over, estimated with the opened tips of a pair of standard biopsy forceps which had a span of 5 mm. Two antral biopsy specimens taken from the incisura and the greater curve within 5 cm of the pylorus were subjected to a standard rapid urease test by immersing the specimens in 1 ml 5% urea with phenol red (one drop of 0.1% phenol red in 10 ml 5% urea stock solution) as indicator. The rapid urease test had a sensitivity and specificity of over 90%. The result of the test was read by a research nurse 20 minutes later and was not disclosed to the endoscopist, and if this was positive the patient would be included in the study. Endoscopy, biopsies, and rapid urease tests were performed within 72 hours before the start of treatment, at the end of four weeks of treatment, and, if the ulcer remained incompletely healed, at further four week intervals up to 12 weeks. Healing was defined as complete disappearance of the ulcer and non-healing as persistence of ulcer, however small. If the size of the ulcer at reassessment endoscopy was estimated to have reduced by less than 50%, remained unchanged, or become larger, the patient would be withdrawn from the study and given standard antiulcer treatment.

STUDY DESIGN AND MEDICATIONS

Patients were randomised to receive 300 mg metronidazole, 500 mg amoxycillin, and 250 mg clarithromycin or their placebo four times daily for two weeks. These antibiotics have been shown to be effective for the treatment of H pylori infection when combined with a colloidal bismuth subcitrate, proton pump inhibitors, or sucralfate. The active medications or starch (as placebo) were packed in gelatin capsules by the hospital pharmacists, so that the antibiotic capsules and their respective placebo capsules were identical in appearance and taste. Each patient took three capsules four times daily, after meals and at bedtime, for two weeks. It was anticipated that patients on antibiotic treatment might develop dyspeptic side effects, and if both groups were allowed to take antacids when necessary for ulcer pain, the antibiotic group might have an increased tendency to take more antacids and therefore to have better ulcer healing rates, as antacid

**Table 1** Patient characteristics in the two groups, and in those with healed and unhealed duodenal ulcer at the end of four weeks

<table>
<thead>
<tr>
<th>Clinical characteristics:</th>
<th>4 weeks</th>
<th>Placebo</th>
<th>p Value</th>
<th>Healed 4 weeks</th>
<th>Unhealed 4 weeks</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>50.4 ± 2.2</td>
<td>47.4 ± 2.2</td>
<td>0.072</td>
<td>48.1 ± 2.1</td>
<td>48.9 ± 2.6</td>
<td>0.82</td>
</tr>
<tr>
<td>Male (%)</td>
<td>67.6 ± 6.4</td>
<td>64.6 ± 4.4</td>
<td>0.64</td>
<td>67.3 ± 6.2</td>
<td>62.1 ± 4.4</td>
<td>0.64</td>
</tr>
<tr>
<td>Age of onset of ulcer symptoms (y)</td>
<td>38.3 ± 2.4</td>
<td>36.1 ± 2.6</td>
<td>0.08</td>
<td>36.7 ± 2.2</td>
<td>37.8 ± 3.5</td>
<td>0.79</td>
</tr>
<tr>
<td>Duration of ulcer symptoms (y)</td>
<td>9.5 ± 1.7</td>
<td>9.8 ± 1.8</td>
<td>0.35</td>
<td>9.7 ± 1.7</td>
<td>11.0 ± 2.2</td>
<td>0.66</td>
</tr>
<tr>
<td>Current period (months)</td>
<td>24 ± 7 (49)</td>
<td>23 ± 8 (49)</td>
<td>0.0</td>
<td>20.4 ± 7 (33)</td>
<td>31.3 ± 18 (33)</td>
<td>0.44</td>
</tr>
<tr>
<td>Latest remission period (months)</td>
<td>2.0 ± 0.4</td>
<td>2.7 ± 1.3</td>
<td>0.52</td>
<td>3.5 ± 1.2</td>
<td>2.9 ± 0.9</td>
<td>0.69</td>
</tr>
<tr>
<td>Pain score (range: 0-10)</td>
<td>1.1 ± 0.1</td>
<td>1.2 ± 0.3</td>
<td>0.79</td>
<td>1.1 ± 0.1</td>
<td>1.2 ± 0.2</td>
<td>0.40</td>
</tr>
<tr>
<td>Average pain duration (h)</td>
<td>2.2 ± 0.6</td>
<td>2.3 ± 0.7</td>
<td>0.79</td>
<td>2.4 ± 0.7</td>
<td>2.1 ± 0.7</td>
<td>0.79</td>
</tr>
<tr>
<td>Back pain (%)</td>
<td>22.7 ± 7.9</td>
<td>22 ± 2.9</td>
<td>0.09</td>
<td>19.2 ± 7.9</td>
<td>27.6 ± 4.0</td>
<td>0.40</td>
</tr>
<tr>
<td>Nocturnal pain (%)</td>
<td>53.3 ± 13.6</td>
<td>51.9 ± 13.6</td>
<td>0.16</td>
<td>51.9 ± 13.6</td>
<td>69.0 ± 13.6</td>
<td>0.12</td>
</tr>
<tr>
<td>Previous melena (%)</td>
<td>41.9 ± 32.8</td>
<td>40.4 ± 40.4</td>
<td>0.34</td>
<td>34.4 ± 34.4</td>
<td>37.8 ± 37.8</td>
<td>0.78</td>
</tr>
<tr>
<td>Previous haematemesis (%)</td>
<td>4.5 ± 4.0</td>
<td>4.0 ± 6.2</td>
<td>0.58</td>
<td>5.8 ± 3.5</td>
<td>3.5 ± 9.4</td>
<td>0.94</td>
</tr>
</tbody>
</table>

**Personal characteristics:**

- Work stress (score 0-3)
  - 0.5 ± 0.1
  - 0.7 ± 0.1
  - 0.08
  - 0.5 ± 0.1
  - 0.7 ± 0.1
  - 0.21
- Neurosis (score 0-3)
  - 1 ± 0.2
  - 0.7 ± 0.1
  - 0.33
  - 0.8 ± 0.1
  - 0.7 ± 0.2
  - 0.48
- Cigarettes:
  - Non-smoker (%)
    - 75.6
    - 77.8
    - 0.4
    - 80.4
    - 75.9
    - 0.81
  - <10/day (%)
    - 67.3
    - 63.3
    - 0.39
    - 39.6
    - 13.8
    - 0.23
  - 10-20/day (%)
    - 17.8
    - 8.9
    - 0.1
    - 17.3
    - 6.9
    - 0.33
  - Alcohol use (%)
    - 67.7
    - 11.1
    - 0.13
    - 11.5
    - 3.4
    - 0.21
  - Habitual analgesics (%)
    - 2.2
    - 4.4
    - 0.28
    - 3.8
    - 0.28
  - Familial dyspepsia (%)
    - 29.4
    - 32.8
    - 0.17
    - 26.4
    - 13.5
    - 0.66
  - Strength (score 0-3)
    - 0.7 ± 0.1
    - 0.9 ± 1.7
    - 0.24
    - 0.7 ± 1.4
    - 0.8 ± 1.9
    - 0.42
  - Body weight (kg)
    - 61.3 ± 7.3
    - 61.8 ± 2.3
    - 0.35
    - 61.2 ± 1.5
    - 61.9 ± 1.7
    - 0.80
  - Blood group O (%)
    - 70.8
    - 57.1
    - 0.23
    - 61.5
    - 65.5
    - 0.91

**Endoscopic characteristics:**

- Ulcer site:
  - Anterior (%)
    - 64.4
    - 73.3
    - 0.18
    - 57.7
    - 79.3
    - 0.05
  - Posterior (%)
    - 8.9
    - 6.7
    - 0.2
    - 11.5
    - 3.4
    - 0.21
  - Right (%)
    - 8.9
    - 6.7
    - 0.2
    - 11.5
    - 3.4
    - 0.21
  - Floor (%)
    - 17.8
    - 11.1
    - 0.16
    - 17.3
    - 10.3
    - 0.40
  - Multiple ulcers (%)
    - 24.4
    - 13.3
    - 0.09
    - 19.2
    - 13.8
    - 0.36
- Index ulcer:
  - Diameter (mm)
    - 7.1 ± 0.3
    - 7.0 ± 0.4
    - 0.88
    - 6.8 ± 0.3
    - 7.4 ± 0.6
    - 0.34
  - Depth (mm)
    - 1.5 ± 0.1
    - 1.0 ± 0.1
    - 0.24
    - 1.3 ± 0.1
    - 1.3 ± 0.1
    - 0.04
  - Surrounding inflammation (score 0-3)
    - 1.2 ± 0.1
    - 1.2 ± 0.1
    - 0.70
    - 1.1 ± 0.1
    - 1.3 ± 0.1
    - 0.35
  - Deformity (score 0-3)
    - 0.9 ± 0.1
    - 0.8 ± 0.1
    - 0.44
    - 0.79 ± 0.1
    - 1.0 ± 0.2
    - 0.34

Values with parentheses are means (SD).
Antibiotics for duodenal ulcer. Thus to have maximal alleviation of the dyspeptic symptoms related to ulcer or side effects of the medications, patients were asked to take 500 mg acetaminophen when necessary, and if this did not help within an hour, two antacid tablets (Gelusil (Parke-Davis, Santurce, PR) containing 500 mg magnesium trisilicate and 250 mg dried aluminium hydroxide gel with a neutralising capacity of 6 mEq HCl) by chewing, both medications being allowed up to three times a day. Acetaminophen has no harmful effects on gastrointestinal mucosa. Patients were asked to record their symptoms and use of medications on a diary card, to return all remaining medications at follow up, and to report to the research nurses by phone or in person when symptoms were severe or when side effects, including diarrhoea, occurred. The nurses would assess the situation and would as far as possible encourage them to continue with the treatment. At the end of four weeks, patients were interviewed by the research nurses for progress of symptoms and side effects of treatment. The returned medications were counted and the results recorded. Informed consent was obtained from all patients, and the protocol for the use of antibiotics and placebo had been approved by the ethics committee, Faculty of Medicine, University of Hong Kong in 1991.

13C-urea breath test A 13C-urea breath test for the detection of H pylori infection was performed on all patients eight weeks after the start of treatment. The 13C-urea breath test was preferred at this stage because it avoided the need for an endoscopy. Briefly, after an overnight fast, a breath sample was collected in a sterile vacutainer. The patient then took a test drink containing 75 mg 13C-urea dissolved in 50 ml water, and underwent various simple postural positioning manoeuvres to allow contact of the solution with the various parts of the stomach. A second breath sample was collected 30 minutes after the drink. The results of the breath test theoretically, therefore, represented the H pylori status of the stomach as a whole. The 13C was analysed with a purpose designed mass spectrometer (Fisons, Manchester, UK); the sensitivity and specificity of the test was 90–100%. The results of the breath tests were not disclosed to the investigators, including the research nurses and endoscopists.

STATISTICAL DESIGN AND ANALYSIS Based on the assumption that 70% of the antibiotic treated patients and on previous experience about 35% of the placebo treated patients would have their ulcers healed at four weeks, we estimated that each treatment group should consist of at least 40 patients to show a difference of 35% with a type I error of 0.01 and a type II error of 0.2 (two sided test). The code of each patient was broken by the hospital pharmacist in two stages. In the first stage, the code was broken into the two treatment groups, A or B, without disclosing whether they were taking antibiotics or placebos. The results were analysed by a statistician and presented at a meeting of the ulcer research team, after which the codes for A and B were finally broken. The two stage decoding safeguarded against any possible investigator bias. Values were expressed as mean (SD), analysis of variance (ANOVA) was used for comparison of means, and a two sided Pearson χ2 test was used to compare proportions. The 12 week design also allowed analysis by the life table method. Patients who completed the study were subjected to stepwise discriminant analysis with healed ulcer as the dependent variable and the characteristics listed in table 1, as well as the results of the four week urease test and eight week 13C-urea breath test for H pylori, as the independent variables, using the statistical package for the social sciences (SPSS/PC, SPSS Inc, Chicago, USA) programs. A conditional rule—p IN and p OUT<0.05 —was used to enable the selection of the least number of variables with the best discriminant function. The standardised canonical discriminant function coefficients, as derived from the discriminant analysis, provided additional information on the relative contribution of the selected variables in discriminating patients with healed ulcer from those with unhealed ulcer.

Results DROPOUTS, SIDE EFFECTS, AND COMPLIANCE Ninety seven of 100 consecutive patients with endoscopically active duodenal ulcer had a positive rapid urease test and were admitted into the study. Forty eight and 49 patients were randomised to receive antibiotics and placebos respectively; of these, eight patients in each arm did not complete the study and table 2 lists the reasons. Non-compliance as assessed from the diary records and by return drug counts was negligible in both groups (table 2).

HEALING EFFICACY AND H PYLORI CLEARANCE AND ERADICATION Two weeks of treatment with antibiotics resulted in 92.5% healing at four weeks and 100% at eight and 12 weeks; the corresponding healing rates for placebo treatment were 30.6%, 51%, and 53.1%, the differences between the two treatment groups being significant at p<0.001 at each time point. These were also significant by life table analysis, which took into consideration all patients who had dropped out (fig 1 and table 2). The differences remained significant when all patients admitted to the study—the intent to treat patients—were analysed (table 2). Two weeks of antibiotic treatment also resulted in 85% clearance and 62.9% eradication of H pylori infection, as determined respectively by a negative urease test of antral biopsy specimens at four weeks and a negative 13C-urea breath test.
test at eight weeks; the corresponding rates for placebo treatment were 12.2% and 9.8% respectively. The differences were also significant at p<0.001 (table 2). Symptomatic improvement was significantly greater in the antibiotic group than in the placebo group (fig 2), and the consumption of acetaminophen and antacids was also significantly less (p<0.04 for both; table 2).

**Factors affecting healing**

The duodenal ulcers healed in 87.2% of patients in whom *H pylori* clearance was achieved, and in 86.2% of those in whom eradication was successful, compared with 42.9% and 51.9% respectively in those who failed to reach these end points (p<0.001 and <0.003 respectively; table 3). The persistence of *H pylori* at four weeks or eight weeks did not affect the superiority of antibiotics over placebo in the healing of duodenal ulcer (table 3).

**Discussion**

This double blind, placebo controlled study showed for the first time that a two week antibiotic regimen designed to treat *H pylori* infection and consisting of metronidazole, amoxicillin, and clarithromycin, without any accompanying known antiulcer agent, was effective for the healing of duodenal ulcer. The healing rates at four weeks were 92.5% and 36.6% for the antibiotics and the placebo respectively (fig 1). Two weeks after treatment, antral biopsy specimens became *H pylori* negative in 85% of the antibiotic group; this has been referred to as the clearance rate of *H pylori*.³ It is likely that part of the clearance was related to the suppression of the infection,
because six weeks after treatment, the negative rate as determined by the \(^{13}\)C-urea breath test was 62.5%; this corresponded to the eradication rate of the infection described in the literature, which was arrived at after an interval of four weeks or more between the completion of treatment and the test.\(^6\) Both of these results were significantly higher than those after placebo treatment (table 2), indicating that the antibiotic regimen used was effective for the treatment of \(H\) \(pylori\) infection. These results also suggested that clearance or eradication of \(H\) \(pylori\) contributed to the healing of duodenal ulcer. This was further supported by the finding that duodenal ulcer healed in 87.2% and 86.2% of patients in whom \(H\) \(pylori\) clearance or eradication was achieved, versus 42.9% and 51.9% in whom these processes failed (table 3). The stepwise discriminant analysis confirmed that \(H\) \(pylori\) clearance and eradication were both discriminative for duodenal ulcer healing, together with ulcer depth (table 4). Interestingly, the analysis also showed that clearance of the organism contributed more to ulcer healing than eradication (table 4), the second being known to be more associated with ulcer remission.\(^1,3\) Ulcer size had been previously found to affect duodenal ulcer healing.\(^22\) Recent single blind studies comparing regimens containing antibiotics and an antulcer agent such as colloidal bismuth subcitrate or ranitidine against a standard antulcer regimen such as ranitidine or omeprazole suggested that eradication of \(H\) \(pylori\) improved the healing of duodenal ulcer.\(^28\) Unlike placebo controlled trials, studies using a standard antulcer regimen as a control require, for valid statistical purposes, a large number of patients (for example, 350 in each arm for 80% healing) to show that the new treatment has similar efficacy as the standard,\(^25\) and studies with such sample sizes are not available. They are also open to investigator bias,\(^26\) as by simply keeping a high overall endoscopic healing rate (for example, 80%), even though the endoscopist is blinded, this rate will be transmitted to each arm as such, and will lead to the conclusion that the new treatment is as effective as the standard (both being 80%). It is interesting to note that in the 15 patients whose ulcers healed with placebo, most (93.3%) had, as expected, persistence of \(H\) \(pylori\) infection, supporting previous results\(^3\) and indicating the presence of a placebo effect in ulcer healing. This might explain the apparent excess of ulcer healing (92.5%) over that expected from \(H\) \(pylori\) clearance (89%) or eradication (62.5%), if the clearance or eradication alone was responsible for ulcer healing. Placebo treatment did seem to clear and eradicate the organism in a small proportion of patients, an intriguing finding probably related to the limitation of the tests involved, such as biopsy sampling or rapid gastric emptying of the test meal. It is known that multiple factors are responsible for ulcer healing\(^22\) and the results of the present discriminant analysis also support this (table 4). Another interesting finding was the lesser efficacy of the antibiotic regimen relative to that of placebo in the healing of duodenal ulcer, irrespective of whether or not the \(H\) \(pylori\) infection had been cleared or eradicated (table 3). Whereas this might be partly explained by the possibility that the infection was suppressed in some patients and recurred later, another explanation could be that the antibiotics healed duodenal ulcer through mechanisms other than elimination of the infection. This concurred with previous reports that amoxicillin,\(^27\) metronidazole,\(^28\) and furazolidone\(^31\) had been reported to have various successes in the healing of peptic ulcer. Symptomatic relief as assessed by pain score and the proportion of patients who became pain free was achieved significantly better in the antibiotic group than in the placebo group (fig 2). This was supported by the larger mean number of acetaminophen and antacid tablets used in the placebo than in the antibiotic group (table 2). Despite this, however, the dropouts due to intolerable dyspeptic symptoms were similar in the two groups, suggesting that the symptom benefit from antibiotic treatment could be offset by possible antibiotic induced dyspepsia in a subgroup of patients. Although this antibiotic regimen is not ideal for the treatment of duodenal ulcer with its need for multiple dosing and acetaminophen or antacid

### Table 3: Effect of drug treatment and \(H\) \(pylori\) clearance and eradication on the healing of duodenal ulcer at 4 weeks

<table>
<thead>
<tr>
<th>Variables selected</th>
<th>Wilks’ (\eta)</th>
<th>Significance</th>
<th>Standardised canonical coefficients</th>
</tr>
</thead>
<tbody>
<tr>
<td>(H) (pylori) test at 4 weeks, (clearance)</td>
<td>0.818</td>
<td>0.0001</td>
<td>0.6322</td>
</tr>
<tr>
<td>Ulcer depth</td>
<td>0.759</td>
<td>0.0005</td>
<td>0.6067</td>
</tr>
<tr>
<td>(H) (pylori) (^{13})C-urea breath test at week 8, (eradication)</td>
<td>0.692</td>
<td>0.0005</td>
<td>0.5385</td>
</tr>
</tbody>
</table>

The relative contribution of each characteristic can be compared with standardised canonical coefficients, the higher the value, the greater the contribution.
supplement, as well as a 12.5% dropout rate, its success in ulcer healing constitutes the strongest evidence to date that \textit{H} \textit{pylori} infection is aetologically related to duodenal ulceration, and opens up the therapeutic concept of treating \textit{H} \textit{pylori} related duodenal ulcer as an infection and relieving its symptoms with acid reducing agents, such as antacids, \textit{H}2 receptor antagonists, and proton pump inhibitors.

This work was supported by Peptic Ulcer Research Fund (311/40/0722) of the University of Hong Kong. We are grateful to the Queen Mary Hospital Pharmacy for the preparation and randomization of the medications, to Nurse Specialist M Chong, Registered Nurses SM Chan, LYC Fan, HS Lee, GW Wong, and SY Tang for nursing assistance, to Ms E Kwok for technical support, to Ms A Wong for data management, and to Mr Stanley Yeung for statistical calculations.


26. Lam SK. A plea to include a placebo group in ulcer trials. \textit{Gastroenterology} 1983; 85: 983.