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Bismuth Subsalicylate Suppression of *Helicobacter pylori* in Nonulcer Dyspepsia: A Double-Blind Placebo-Controlled Trial

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Gastritis caused by Helicobacter pylori *(HP) is common in patients with nonulcer dyspepsia (NUD), but an etiologic relationship between the histologic lesion and clinical symptoms is unproven. HP is inhibited by bismuth subsalicylate (BSS), a traditional remedy for dyspeptic complaints. The aim of this study was to assess the short- and long-term effects of BSS on HP, gastritis, and symptoms in patients with NUD. One hundred twenty-six patients with NUD who were shown to be infected with* H. pylori *(HP+) were enrolled. There was a two-week placebo run-in period to eliminate placebo responders. Fifty patients remained symptomatic and were randomly assigned to therapy with either BSS liquid or a matching placebo. EGD, biopsy, and clinical evaluations were performed at entry, at week 5 (end of therapy), at week 9 (four weeks after therapy), or at time of symptomatic relapse. Twenty-seven patients received placebo and 23 patients received BSS. BSS suppressed* H. pylori *in 15/23 patients (65%) and eradicated it in one patient, whereas the placebo had no effect on* H. pylori. *Gastritis improved during therapy with BSS but relapsed by week 9. There was no significant change in level of dyspeptic symptoms during or after treatment, although one month after the end of treatment, the patients in the BSS group consistently had lower symptom scores and fewer symptomatic days for all symptoms measured. The study confirms that BSS given for three weeks suppresses but does not usually eradicate* H. pylori. *Such short-term suppression of* H. pylori *heals gastritis but does not result in clinical improvement.*

Non-ulcer dyspepsia (NUD) is an ill-defined clinical syndrome in which epigastric "ulcerlike" discomfort is present, but a peptic ulcer is not found (1–3). NUD may be caused by esophageal reflux, gastric motility disorders, irritable bowel syndrome, biliary dyskinesia, pancreatic disease, and perhaps gastroduodenitis (1–3). Several investigators have noted the presence of *H. pylori* in patients with NUD (4–7), but the prevalence varies widely depending on the population studied. For example, in Virginia, Dye et al found 40% of patients with normal endoscopy have *H. pylori* (8), whereas in Italy 60–70% of endoscopically normal patients had the organism (9), and in Kuwait the figure was 96% (10). It has been proposed, therefore, that histologic gastritis is part of the spectrum of peptic ulcer disease and may cause dyspeptic symptoms in the absence of macroscopic ulcer craters (11, 12). It is well known that bismuth salts inhibit *H. pylori* (13–15) and several earlier double-blind studies were

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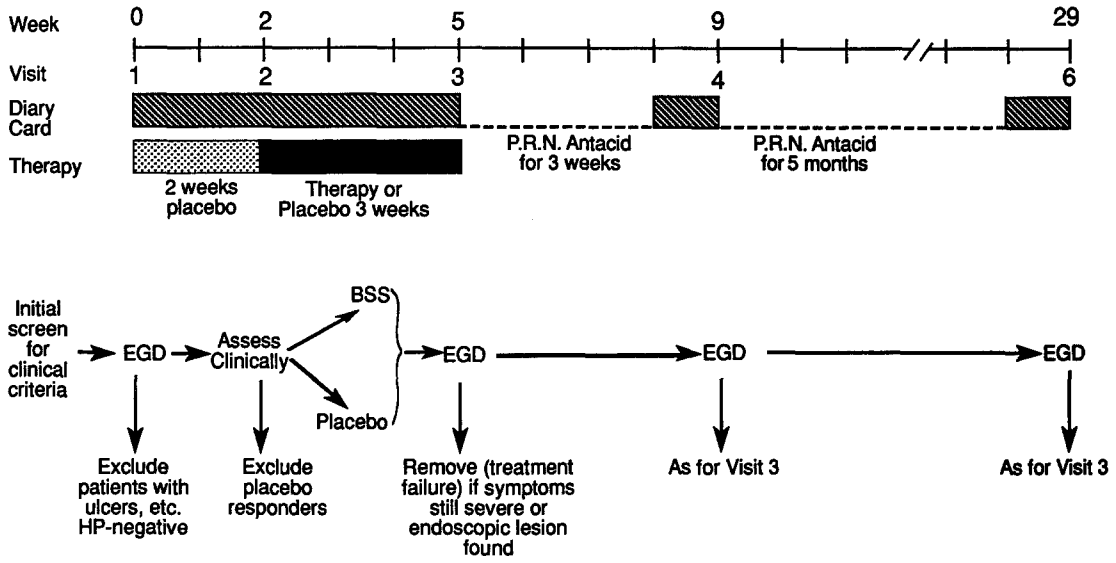

Fig 1. Time line of the study.

able to demonstrate healing of gastritis during treatment with bismuth subsalicylate (16, 17), although clinical improvement was not demonstrated. The aim of this study was to perform a double-blind placebo-controlled trial of bismuth subsalicylate to observe the acute and long-term (three to six months) effects of *H. pylori* suppression on the clinical syndrome of NUD.

MATERIALS AND METHODS

The study was approved by the respective human investigation committees, and all patients signed informed consent. Patients were recruited from the gastroenterology clinic and from advertisements placed in the local press. To qualify for admission to the study, patients were required to be between the ages of 18 and 70 years and must have had persistent, epigastric discomfort for at least one month of sufficient severity to warrant investigation by upper gastrointestinal series and/or endoscopy. Excluded from the study were patients with a history of allergy to aspirin, salicylates, or bismuth, who required continuing therapy with salicylates, corticosteroids, nonsteroidal antiinflammatory drugs, or anticoagulants. Also excluded were patients with proven gastric or duodenal ulcers within the preceding six months, those taking H_2 receptor antagonist therapy for previous ulcer disease, or those known to have systemic cancer, irritable bowel syndrome, endoscopic esophagitis, previous gastric surgery, or biliary tract disease. Excluded medications during the study were salicylates, aspirin, H_2 receptor antagonists, NSAIDs, antacids, tricyclic antidepressants, anticholinergics, bismuth-containing drugs, and antibiotics.

To qualify for screening endoscopy prior to entry into the study, patients were required to have a consistent level of moderately severe dyspepsia defined as a score of 5 or more (out of 10) on a linear scale for any one of the following five symptoms: stomach pain, heartburn, nausea, bloating or belching, and overall stomach symptoms. Patients whose symptoms were not clearly gastric were screened with ultrasound to exclude gallstones. Patients who fitted the clinical criteria for entry underwent endoscopy. As described above, patients with major endoscopic lesions (eg, ulcers, multiple erosions, esophagitis) or preexisting gastric surgery were excluded. Following examination of the esophagus, stomach, and duodenal bulb, biopsy specimens were taken from the antral mucosa to examine for gastritis and *Helicobacter pylori*. Two samples from the antrum were fixed in formalin and stained with hematoxylin and eosin and Giemsa. One sample was placed in a drop of normal saline and refrigerated until transfer to the microbiology laboratory for culture using standard methodology (18).

H. pylori-positive patients who qualified were entered into an initial placebo phase of the study (Figure 1). At this time all patients were told that they had been randomized to either active therapy or placebo. For two weeks patients took medication (a white suspension of titanium dioxide flavored to appear identical to the active medication), 15 ml four times daily 30–60 min before meals. Symptoms were recorded on a daily basis with diary cards and scored on a linear scale for the five symptoms described above. Before patients started in the study (week 0), blood was taken for CBC, renal function, liver function, and prothrombin time. At the end of each monitoring period noncompliant patients were removed from the study.

After two weeks on placebo medication, patients with continuing symptoms of at least moderate intensity were randomized to therapy with either BSS or placebo and continued in the study. The dose of bismuth subsalicylate used was 512 mg (equivalent to two tablets or 30 ml of standard strength Pepto-Bismol) four times a day. Prior to commencing drug, blood was drawn for serum bismuth estimation. The medication (BSS or placebo) was given

for a further three weeks (weeks 2–5), and daily diary cards were recorded as before.

At the end of week 5, patients attended for a second endoscopy and laboratory work-up. Patients completed the study as treatment failures if a major endoscopic lesion was present or if symptoms were still severe and had not responded to therapy. Patients who felt well and in whom the endoscopy was normal ceased all medication and were scheduled for a further follow-up endoscopy at week 9. During week 9 they were instructed to fill out their daily diary cards and return them at the week 9 visit. Patients who were well at week 9 remained in the study until a final follow-up endoscopy six months after treatment (week 29) or sooner if clinical relapse occurred.

Histological Methods. Biopsies were scored on an ordinal scale of 0–3+ for mononuclear cells, polymorphs, mucus depletion, and *H. pylori* organisms. Gastritis was said to be present if the sum of the mononuclear cells and polymorphonuclear cells was >2.

Statistical Analysis. For the purpose of comparing symptoms, the following variables were computed and analyzed for each symptom: (1) maximum severity of each symptom within one week before a given visit; (2) the number of days with a symptom and the number of days with a severe symptom in the week before a visit (a severe symptom is defined as a score of at least 3 for that symptom); (3) change in the maximum symptom score from baseline to visits 3 and 4; (4) change from baseline in the number of days with a symptom in the week prior to a given visit for visits 3 and 4; and (5) changes from baseline in number of days with a severe symptom at visits 3 and 4.

A retrospective analysis of the data revealed that, because of the extreme variability of symptoms, the power of this study to detect a significant change (in this group of patients) was only 0.4 at randomization. Power decreased in later parts of the study because of dropouts.

RESULTS

Suppression of *H. pylori*. After three weeks of BSS therapy, *H. pylori* was absent and gastritis was healed in 15 of 23 patients (65%). In the placebo group, gastritis persisted in 26 of 27 patients (96%), $P < 0.0001$. At week 9 (four weeks after treatment) and subsequent assessments, *H. pylori* was present in all placebo-treated patients and in all but one of the BSS-treated patients. Thus, BSS therapy cleared *H. pylori* from the gastric mucosa in approximately 70% of patients but achieved eradication in only 4% of patients. The histologic appearance of the gastritis improved in parallel with reduction in *H. pylori* numbers (Figure 2).

Symptom Assessment. The Wilcoxon (rank sum) test and two sample *t* tests were used to compare the effect of BSS treatment to the effect of placebo treatment on the above variables. A significance level of 0.05 was used for each comparison. For each symptom and visit, the tests of treatment effects on all of the above variables showed no significant difference between placebo and Pepto-Bismol treatment groups at an alpha level of 0.05. However, one month after the end of treatment (week 9), the patients in the bismuth group consistently had numerically lower symptom scores and fewer days with symptoms for all symptoms measured. It was also seen that symptom scores in both treatments tended to decrease over time. Examples of symptom changes are given in Figure 3, which shows severe symptom days by therapy and symptom. Note that the very wide confidence intervals made it difficult to achieve significance in a study of this size.

Antacid use was numerically less in patients cleared of *H. pylori* during week 5 (1.27 ± 0.118 SEM vs. 1.56 ± 0.121 SEM for BSS and placebo, respectively). This difference was not significant ($P = 0.1$).

Safety of Bismuth Subsalicylate During Treatment Phase. In the actively treated group, small changes in alkaline phosphatase (−5 units) and SGOT (+4 units) were seen within the normal range. These were not thought to be clinically significant. Bismuth levels remained within safe levels during the study (mean 6.68 μg/liter, ± 4.18 SD max 15.00).

DISCUSSION

There are now several double-blind studies reported in the literature in which *H. pylori* suppression has been attempted with either bismuth subsalicylate and/or antibiotic combination for the treatment of NUD. As with our study, Lanza et al (16) demonstrated healing of gastritis and suppression of *H. pylori*, but they did not repeat biopsy four weeks after therapy and so could not document recrudescence of the infection. We have shown that suppression of *H. pylori* was only temporary when patients were given bismuth subsalicylate alone and that both gastritis and the bacteria reappeared one month later. McNulty et al (19) also failed to show significant benefit when *H. pylori* was treated with BSS or with erythromycin ethylsuccinate suspension (which did not inhibit *H. pylori* as effectively). In that study there was a marked improvement of symptoms in the placebo group (65%), thus making clinical benefit with BSS very difficult to demonstrate. Our collection of clinical data was modeled on experience obtained in McNulty's study. Several investigators have shown that there is no definitive *H. pylori*-associated syndrome and, there-

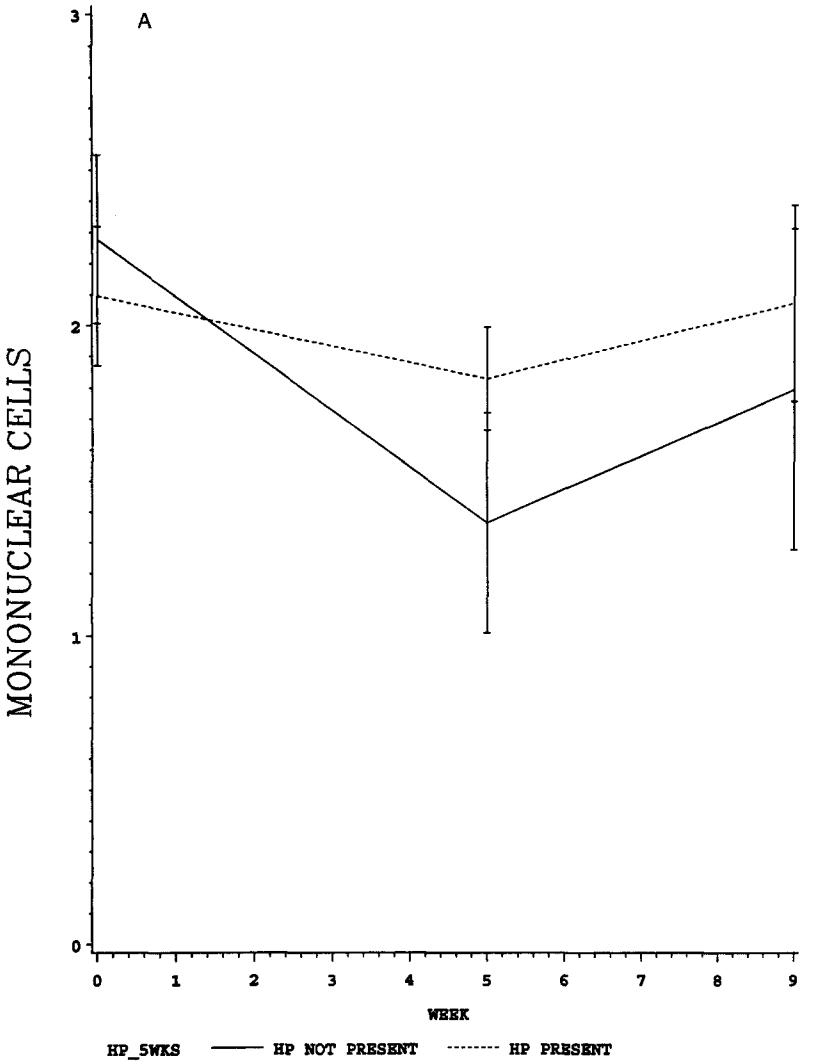

Fig 2. Histological Changes (A) Mononuclear cells. They decreased slightly with suppression of *H. pylori* (solid line). (B) Neutrophils. A highly significant change was seen in neutrophil score when *H. pylori* was suppressed (solid line week 5). Graph shows mean ±95% CI.

fore, like others, we were obliged to pick a number of symptoms for study that were appropriate for a broad range of patients with dyspepsia and gastritis.

Studies that used colloidal bismuth subcitrate (CBS, DeNol) to inhibit and/or eradicate *H. pylori* have been more successful in demonstrating a clinical benefit. Rokkas et al (20) noted improvement in symptoms that was marginal at the end of three weeks but became highly significant when patients were treated for six weeks. Similarly, both Lambert et al (21) and Kang et al (22) saw improved symptoms during a second month of treatment with CBS. Loffeld et al (23), on the other hand, did not see a major benefit over placebo when *H. pylori* patients were treated with CBS, except for a modest improvement in the symptom of nausea.

In retrospect, there were several methodologic problems with prior studies. As with our study, they did not use a placebo that stained the stools black, so it was possible for patients to discover the actual treatment being prescribed. Secondly, in most of the previous studies, patients with NUD were entered regardless of *H. pylori* status, so that many *H. pylori*-negative patients were randomized to therapy. This had the useful effect of showing in three studies (20–22) that *H. pylori*-negative patients with NUD did not respond to bismuth therapy. These studies, although observing a significant

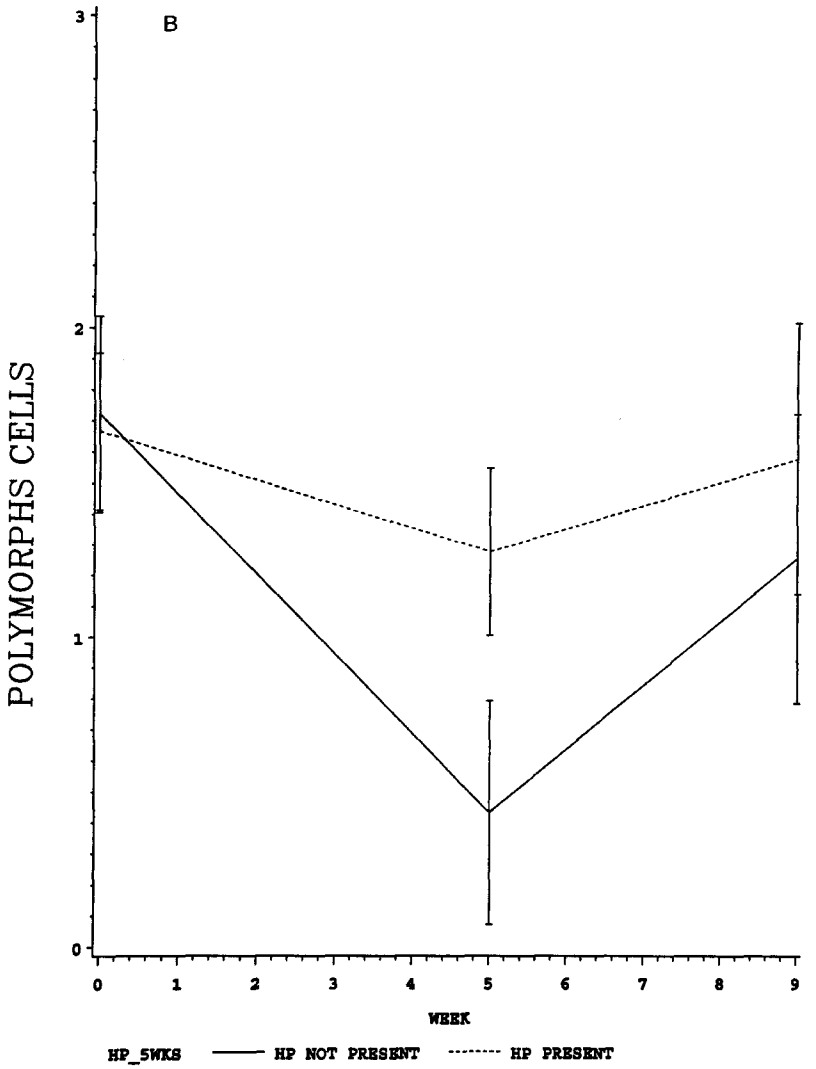

Fig 2. Continued.

improvement in symptoms with CBS therapy, had potentially large type 2 (β) statistical errors because of the relatively small number of *H. pylori*-positive patients actually given active therapy. The study of Loffeld et al (23) also had the potential for a large β error since that study only included 50 randomized patients.

We had hoped to avoid these problems in our study, but several practical considerations caused very slow recruitment. The remuneration ($250.00) was insufficient to motivate the patients to stay in the study, the study was of long duration, rather complicated, restrictive in its list of excluded medications, and the therapy used was not very effective. For these reasons, the study was stopped after 50 patients had qualified for analysis. At this stage, even if some benefit was present, it could not have been sufficient to justify a rather inconvenient therapy. In addition, the evidence that *H. pylori* was only suppressed, rather than eradicated, suggested to us that more effective antibacterial regimens would be required to test the hypothesis that *H. pylori* was unrelated to NUD.

Our conclusion from the study is that suppression of *H. pylori* with three weeks of therapy of bismuth subsalicylate is ineffective at relieving NUD symptoms. Interestingly, the apparent slight trend towards improvement in the four weeks after therapy suggests that gradual resolution of symptoms might have occurred in these patients if *H. pylori* was permanently eradicated. In future studies, therefore, we plan a shorter therapy and will combine

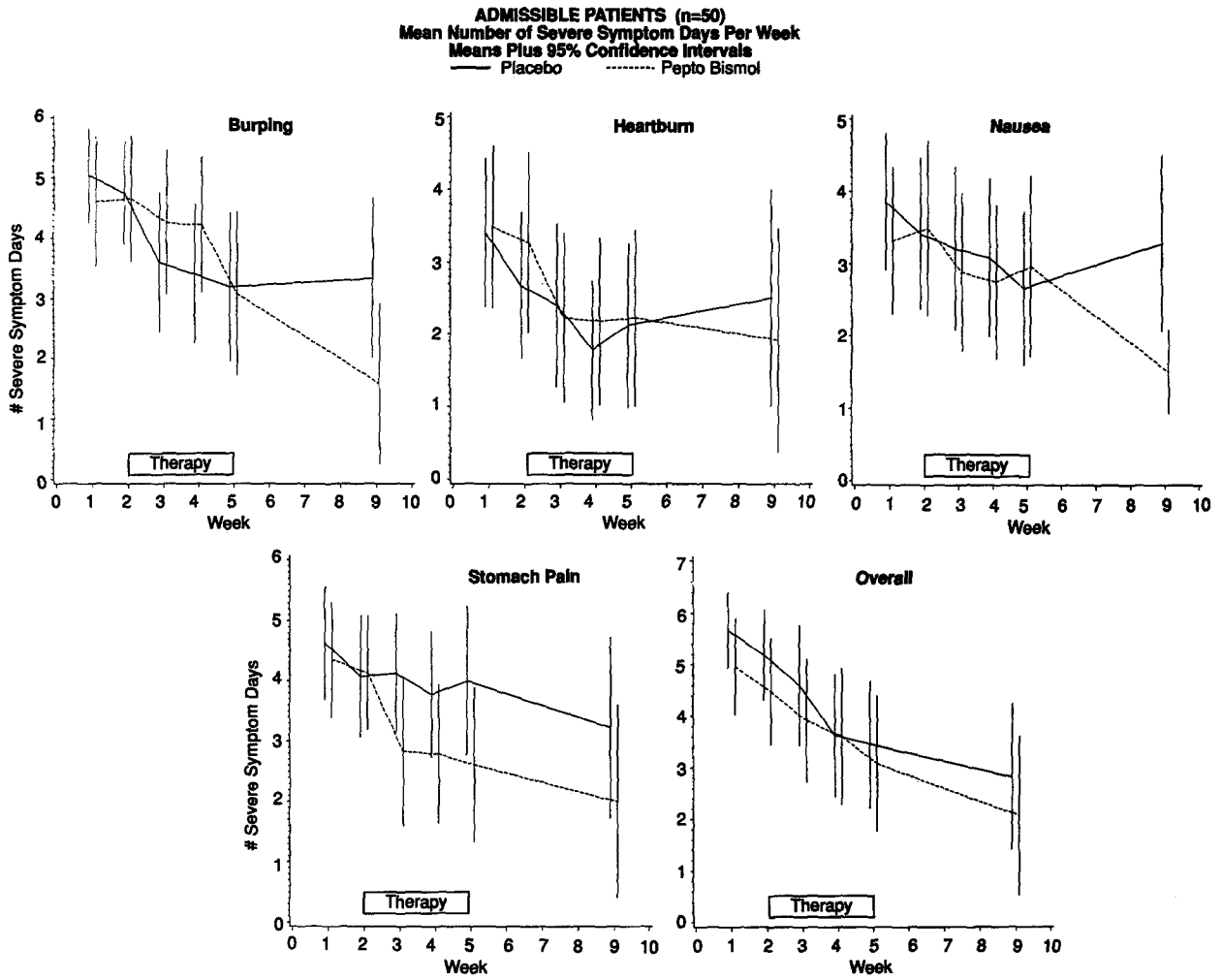

Fig 3. Examples of symptom changes by therapy and symptom.

antibiotics with bismuth in the hope that *H. pylori* infection can be cured. In addition, we suggest an observation period of one year in order to detect gradual long-term clinical improvement.

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