Approach to Treatment of Dyspepsia in Primary Care

A Randomized Trial Comparing “Test-and-Treat” With Prompt Endoscopy

Nicolaas L. A. Arents, MD; Jacob C. Thijs, MD, PhD; Anton A. van Zwet, MD, PhD; Marco Oudkerk Pool, MD, PhD; Jan-Mark Götz, MD, PhD; Ger T. van de Werf, MD, PhD; Klaas Reenders, MD, PhD; Wim J. Sluiter, MD, PhD; Jan H. Kleibeuker, MD, PhD

Background: The value of the “test-and-treat” strategy in the approach to dyspepsia has been evaluated only in a few secondary care studies. Most patients with dyspepsia, however, are treated by their primary care physician. This study evaluated the test-and-treat strategy in primary care.

Methods: Patients consulting their general practitioners for dyspepsia were randomized to either direct open-access endoscopy with Helicobacter pylori testing or a test-and-treat strategy by H pylori serology. In the 12-month follow-up period, any additional treatment or referral for investigations was left at the discretion of the general practitioner. At the end of the study, data were collected concerning the number of endoscopies, changes in symptom severity and quality of life, patient satisfaction, and the use of medical resources.

Results: Two hundred seventy patients were enrolled (129 who received endoscopy and 141 in the test-and-treat group). The prevalence of H pylori infection was 38.3% and 37.2% in the test-and-treat and endoscopy groups, respectively. In the test-and-treat group, 46 patients (33%) were referred for endoscopy during follow-up. Improvement in symptom severity, quality of life, and patient satisfaction was comparable in both groups. Patients in the test-and-treat group paid more dyspepsia-related visits to their general practitioner (P = .005). Patients in the endoscopy group were more often prescribed proton pump inhibitors (P = .007), whereas patients in the test-and-treat group were more often prescribed prokinetic drugs (P = .005).

Conclusions: The test-and-treat strategy proved to be as effective and safe as prompt endoscopy. Only a minority of patients were referred for endoscopy after the test-and-treat approach.

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According to the Rome I criteria, dyspepsia was defined as persistent or recurrent pain or discomfort centered in the upper abdomen. Patients consulting any of the 56 participating GPs for dyspepsia were eligible for the study if the GP considered the symptoms severe enough to warrant endoscopy or the prescription of acid-suppressive medication. The GPs were instructed not to include patients with symptoms suggestive of GERD (heartburn or acid regurgitation as the only or predominant symptom). Other exclusion criteria were age younger than 18 years; the presence of sinister symptoms (including the first appearance of dyspeptic symptoms after the age of 55 years); previously documented PUD or GERD; previous surgery of the upper alimentary tract, other than uncomplicated cholecystectomy; previous anti–H pylori treatment; the use of proton pump inhibitors (PPIs), bismuth compounds, or antibiotics in the month before inclusion; the use of nonsteroidal anti-inflammatory drugs other than low-dose aspirin in the preceding 2 weeks; known allergy to the drugs used in the study; suspected poor compliance; pregnancy or lactation; and participation in any other study. Patients were withdrawn from the study if any malignancy was diagnosed or if the patient became pregnant. After giving written informed consent, patients were randomized by their GP. Randomization was stratified for each GP by supplying the GP with blocks of 4 sealed envelopes, ensuring 2 patients randomized to the test-and-treat group and 2 patients to the endoscopy group.

In the endoscopy group, the patients were referred for open-access endoscopy, which was performed within 2 weeks after inclusion. At endoscopy, 3 biopsy samples were taken within 2 cm of the pylorus for H pylori culture (1 sample) and histologic examination (hematoxylin-eosin staining and either Giemsa staining or immunostaining for H pylori) (2 samples). Antibiotic susceptibility for metronidazole (resistant if minimal inhibitory concentration is \( \geq 8 \)) and clarithromycin (resistant if minimal inhibitory concentration is \( \geq 2 \)) was tested by E-test (AB-Biodisk, Solna, Sweden). A venous blood sample was drawn for the detection of anti–H pylori IgG antibodies by means of a commercially available assay (Pyloriset ELA-G III; Orion Diagnostica, Espoo, Finland). This assay has shown a sensitivity and specificity of 98.4% and 88.4%, respectively, in a previous study performed in the same region. A peptic ulcer was defined as a mucosal break of greater than 5 mm with a clearly visible ulcer crater in either the stomach or the duodenal bulb. Erosive inflammation of the duodenal bulb was considered to be an appearance of PUD. If PUD was detected at endoscopy, the patient was prescribed ranitidine hydrochloride immediately after endoscopy. Patients with reflux esophagitis were prescribed lansoprazole for a period of 3 months. The dosages were left at the discretion of the endoscopist. In all other cases, the patients were referred back to their GP awaiting culture and histology results. All H pylori–infected patients (either culture or histology positive) received a 1-week anti–H pylori regimen guided by susceptibility testing: lansoprazole (30 mg twice daily), amoxicillin (1000 mg twice daily), and either metronidazole (500 mg twice daily) if metronidazole sensitive or clarithromycin (500 mg twice daily) if metronidazole resistant. If susceptibility was not tested, the microorganism was considered metronidazole resistant. In a previous study, performed in the same region, resistance of H pylori to clarithromycin was shown to be very rare (about 2%). If a patient had normal endoscopic findings and was H pylori negative, cisapride (20 mg twice daily) was prescribed for 4 weeks by the GP according to protocol. Peptic ulcers, erosive gastritis, and erosive duodenitis in the absence of H pylori infection were treated after conferring with the gastroenterologist, usually with acid-suppressive agents.

In the test-and-treat group, a venous blood sample was drawn for H pylori serologic testing. If results of testing were positive, the patients were prescribed the combination of lansoprazole, amoxicillin, and clarithromycin by the GP. If negative, the GPs were encouraged to prescribe cisapride (20 mg twice daily) for 4 weeks after endoscopy. If a patient had normal endoscopic findings and was H pylori negative, cisapride (20 mg twice daily) was prescribed for 4 weeks by the GP according to protocol. Peptic ulcers, erosive gastritis, and erosive duodenitis in the absence of H pylori infection were treated after conferring with the gastroenterologist, usually with acid-suppressive agents.

After the initial treatment according to protocol, the GP was free to treat the patient according to his or her own insights. This could include a change in treatment; referral for diagnostic tests, including endoscopy; or referral to a gastroenterologist or another specialist.

The patients were followed up for 12 months. At inclusion and at 12 months, patients were asked to complete a dyspepsia questionnaire evaluating the severity of 8 dyspeptic symptoms (pain in the upper part of the abdomen, bloating, nausea, burping or belching, flatulence, heartburn, sour taste, and halitosis) on a 5-point Likert scale. Quality of life was evaluated at inclusion and after 12 months by means of the RAND-36 questionnaire, a validated Dutch translation of the Short Form-36 questionnaire. At 12 months, patients were invited to donate a second blood sample for H pylori serologic testing. Successful H pylori treatment was defined as a decrease in titer of IgG H pylori antibodies of 40% or more. For the detection of a decrease in antibody level, both the entry sample and the 12-month sample were examined in the same run.

Patient satisfaction with medical treatment was evaluated on a 5-point Likert scale. Whenever a patient did not return a questionnaire, he or she was contacted by telephone by one of us (N.L.A.A.) and urged to do so up to 3 times.

At the end of the study, the GPs’ records of each patient (electronic and/or patient charts) were reviewed by a single investigator (N.L.A.A.). Data were collected concerning the number of visits for dyspepsia, the number of visits for other reasons, additional investigations (endoscopy, abdominal ultrasound, and x-ray studies of the gastrointestinal tract), specialist referrals, and hospital admissions. Finally, all pharmacies were asked to provide a printed list of all medications delivered to the patients within the 1-year follow-up period. The dyspepsia-related use of medical resources was calculated for medical consultations, dyspepsia-related investigations, hospital admissions, and dyspepsia-related prescriptions.

Differences in mean scores and mean changes in scores between groups were compared after correction for continuity by the method of Yates and Cochran. Mean changes in score within a group were evaluated after correction for continuity by the method of Pitman. Frequencies were compared by the \( \chi^2 \) test with Yates correction. Differences in continuous variables between groups were studied by the Mann-Whitney test. All tests were 2-sided, with a level of significance of \( P < .05 \).

The study protocol was approved by the medical ethical committee of the University Hospital Groningen, Groningen, the Netherlands.
were not enrolled for the following reasons: failure to return the first questionnaires (n=2), failure to undergo endoscopy (n=4), no biopsy specimens taken at endoscopy (n=2), suspected poor compliance (alcohol abuse [n=1], short stay in the area [n=1]), and presence of sinister symptoms (n=1). Therefore, 270 patients were enrolled, 141 patients in the test-and-treat group and 129 in the endoscopy group. Quality of life, time elapsed since the first appearance of symptoms, and duration of current symptoms were not significantly different between the 2 groups (P ranging between .21 and .98 for all items). The mean score of 1 symptom in the dyspepsia questionnaire (nausea) was significantly higher in the test-and-treat group (2.09 vs 1.79; P=.04). Mean scores of the other symptoms, however, as well as other baseline characteristics (Table 1) were comparable.

Forty-six patients (32.6%) randomized to the test-and-treat group (16 serologically H pylori positive) were referred for endoscopy during follow-up. One endoscopy was aborted because of lack of cooperation of the patient. The endoscopic diagnoses in the remaining 45 patients as well as in the patients randomized to the endoscopy group are summarized in Figure 2. The endoscopic diagnosis most commonly made in both groups was GERD (test-and-treat group, 31.1%; endoscopy group, 28.7%). The diagnosis of GERD included esophageal erosions (Savary-Miller grade 1 and higher) and/or Barrett metaplasia (n=2). Duodenal ulcer disease (including erosive duodenitis in 4) was found in 1 of the 46 patients in the test-and-treat group and in 10 patients in the endoscopy group (7.8%; 1 patient also had GERD). Gastric ulcer was found in no patient in the test-and-treat group and in 1 patient (0.8%; this patient also had GERD) in the endoscopy group. Erosive gastritis was found in 1 (2.2%) and 3 (2.3%) patients in the test-and-treat and endoscopy groups, respectively. In 3 patients with PUD, both histologic findings and culture were negative for H pylori. One of these patients (test-and-treat group) had been treated for H pylori infection but still showed erosive inflammation of the duodenal bulb. The other 2 patients, randomized to the endoscopy group, both had a duodenal ulcer. In both, serologic findings were negative as well. The H pylori status in all patients who underwent endoscopy is shown in Table 2. In one 54-year-old patient, randomized to the test-and-treat group, a gastric malignancy was diagnosed 3 weeks after inclusion. Further examination showed multiple liver metastases with ascites, and the patient died within 6

![Flow diagram of the study patients.](image1)

![Endoscopic diagnoses in the patients in the test-and-treat group referred for endoscopy (n=45) and the endoscopy group (n=129). Because of rounding, percentages may not total 100. N indicates normal or hiatal hernia only; GERD, gastroesophageal reflux disease; DU, duodenal ulcer; EG, erosive gastritis; GC, gastric cancer; and GU, gastric ulcer.](image2)

Table 1. Baseline Characteristics of Patients in the Test-and-Treat Group and the Endoscopy Group

<table>
<thead>
<tr>
<th></th>
<th>Test-and-Treat Group (n = 141), No. (%)</th>
<th>Endoscopy Group (n = 129), No. (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, y</td>
<td>47</td>
<td>44</td>
<td>.35</td>
</tr>
<tr>
<td>Male sex</td>
<td>70 (49.6)</td>
<td>59 (45.7)</td>
<td>.62</td>
</tr>
<tr>
<td>Smokers</td>
<td>55 (38.9)</td>
<td>47 (36.4)</td>
<td>.75</td>
</tr>
<tr>
<td>Alcohol use (&gt;1 U/d)*</td>
<td>24 (17.0)</td>
<td>22 (17.1)</td>
<td>.87</td>
</tr>
<tr>
<td>Born outside the Netherlands</td>
<td>9 (6.4)</td>
<td>6 (4.7)</td>
<td>.72</td>
</tr>
<tr>
<td>Helicobacter pylori positive</td>
<td>54 (38.3)</td>
<td>48 (37.2)</td>
<td>.95</td>
</tr>
</tbody>
</table>

* A unit of alcohol was defined as a standard glass of beer, wine, spirits, etc (approximately 10 g of alcohol).
months. In both study groups, endoscopy showed no abnormality or just a hiatal hernia in most patients (62.2% and 60.5% in the test-and-treat and endoscopy groups, respectively). Statistical analysis did not show any significant difference in frequencies of endoscopic diagnoses between the 2 study groups (P = .83).

When compared with the biopsy-based detection methods in the endoscopy group (H pylori positive when positive on histologic examination and/or culture), the serologic test showed a sensitivity, specificity, and positive and negative predictive value (with 95% confidence intervals) of 86.7% (73.2%-95.0%), 92.5% (84.4%-97.2%), 86.7% (73.2%-95.0%), and 92.5% (84.4%-97.2%), respectively.

Follow-up data were not available for 17 patients (12.1%) in the test-and-treat group and 9 patients (7.0%) in the endoscopy group (P = .22) for the following reasons: failure to return follow-up questionnaires (n = 22), pregnancy (n = 2), and malignancy (n = 2) diagnosed during follow-up. Besides the patient with gastric cancer mentioned above, Hodgkin disease was diagnosed in another patient. Baseline characteristics (Table 1) and mean symptom severity score of these dropout patients were comparable to the baseline characteristics of the remaining patients.

Symptom changes in both study groups were evaluated by subtracting the scores in the last questionnaire from the scores in the first questionnaire for each symptom. Figure 3 shows the mean change for each symptom in both groups. All symptoms improved during the study period, and improvement was comparable in both study groups.

The scores for the quality-of-life categories evaluated by the RAND-36 questionnaire (change in health, general health perception, bodily pain, energy/fatigue, general mental health, role limitations due to personal or emotional problems, role limitations due to physical health problems, social functioning, and physical functioning) were calculated according to the instructions of the questionnaire’s designers.35 To detect any improvement or worsening within a category, the first quality-of-life scores were subtracted from the 12-month quality-of-life scores. The median score changes for all categories are shown in Figure 4. There was an improvement in most categories in both groups, and the differences between the 2 groups were not statistically significant.

The use of medical resources in each study group is summarized in Table 3. The mean number of dyspepsia-related GP visits was significantly higher in the test-and-treat group (P = .005). In the endoscopy group, more patients were prescribed PPIs (P = .007), making the mean standard daily dosage in this group higher than in the test-and-treat group. The mean standard daily dosage in the patients receiving PPIs, however, was comparable in both groups (P = .71). Sixty-eight percent of the patients in the endoscopy group who were prescribed PPIs had endoscopy-proven GERD. Prokinetic drugs were significantly more often prescribed in the test-and-treat group (P = .005), making the mean standard daily dosage in this group higher than in the endoscopy group. The use of histamine2-receptor antagonists and antacids in both study groups was comparable. In both groups, the same number of patients did not receive any medication for dyspepsia (18.5% and 23.3% for the test-and-treat and endoscopy groups, respectively).
This study showed that prompt endoscopy in patients consulting their primary care physician for dyspepsia led to similar symptom resolution, improvement in quality of life, and patient satisfaction as compared with the test-and-treat strategy. More than two thirds of the patients treated according to the test-and-treat strategy were not referred for endoscopy during a follow-up period of 1 year.

To our knowledge, this is the first study comparing the test-and-treat strategy with prompt endoscopy in a primary care setting. As most dyspeptic patients are entirely treated by their GP, the test-and-treat approach should be evaluated in that setting. Lassen et al15 recently compared the test-and-treat strategy with prompt endoscopy. In that study, however, follow-up was performed completely in a secondary care setting, which may have biased the results. Reassurance and treatment by a gastroenterologist with a special interest in dyspepsia may be more effective than that by a GP, resulting in a decreased use of medical resources and higher patient satisfaction. Our primary care study has several other positive features. After the initial investigation and treatment guidelines, GPs were allowed to treat their patients according to their own insights. Therefore, the outcome of the test-and-treat strategy in our study is presumably very similar to the outcome if a similar approach were followed in daily clinical practice, thus increasing the external validity of the results. Second, all questionnaires regarding symptoms, quality of life, and patient satisfaction were self-administered, avoiding any interpretation bias by the GP. Finally, anti-H pylori treatment was prescribed to all H pylori–infected patients. Although the

**Table 3. Use of Medical Resources in Both Study Groups in the Study Year**

<table>
<thead>
<tr>
<th></th>
<th>Test-and-Treat Group (n = 124)</th>
<th>Endoscopy Group (n = 120)</th>
<th>Difference</th>
<th>P Value/ OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of GP visits</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspepsia-related</td>
<td>3.06 (1-4)</td>
<td>2.28 (1-3)</td>
<td>0.78*</td>
<td>.005</td>
</tr>
<tr>
<td>Dyspepsia-unrelated</td>
<td>2.73 (1-4)</td>
<td>3.03 (1-5)</td>
<td>-0.30</td>
<td>.38</td>
</tr>
<tr>
<td>No. of SDD†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPI</td>
<td>28.9 (0-29)</td>
<td>71.0 (0-99)</td>
<td>-42.1*</td>
<td>.007</td>
</tr>
<tr>
<td>H2RA</td>
<td>22.9 (0-15)</td>
<td>18.8 (0-15)</td>
<td>4.1</td>
<td>.97</td>
</tr>
<tr>
<td>Prokinetics</td>
<td>16.0 (0-20)</td>
<td>11.6 (0-5)</td>
<td>4.4*</td>
<td>.005</td>
</tr>
<tr>
<td>Antacids</td>
<td>8.1 (0-12)</td>
<td>7.8 (0-12)</td>
<td>0.3</td>
<td>.73</td>
</tr>
<tr>
<td>No. of diagnostic tests</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endoscopy</td>
<td>0.35</td>
<td>1.04</td>
<td>-0.69*</td>
<td>.001</td>
</tr>
<tr>
<td>Ultrasonography of upper abdomen</td>
<td>0.14</td>
<td>0.09</td>
<td>0.05</td>
<td>0.6 (0.27-1.41)</td>
</tr>
<tr>
<td>Upper Gi series</td>
<td>0.05</td>
<td>0.05</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>No. of specialist referrals</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspepsia-related</td>
<td>0.05 (0-0)</td>
<td>0.05 (0-0)</td>
<td>0</td>
<td>1.04 (0.32-3.30)</td>
</tr>
<tr>
<td>Dyspepsia-unrelated</td>
<td>0.44 (0-1)</td>
<td>0.36 (0-0)</td>
<td>0.08</td>
<td>0.27 (0.43-1.21)</td>
</tr>
<tr>
<td>No. of hospital admissions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspepsia-related</td>
<td>0.01 (0-0)</td>
<td>0.0 (0)</td>
<td>-0.01</td>
<td>NA</td>
</tr>
<tr>
<td>Dyspepsia-unrelated</td>
<td>0.08 (0-0)</td>
<td>0.08 (0-0)</td>
<td>0</td>
<td>0.92 (0.36-2.36)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; Gi, gastrointestinal; GP, general practitioner; H2RA, histamine2-receptor antagonist; NA, not applicable; OR, odds ratio; PPI, proton pump inhibitor; SDD, standard daily dosage.

*Significant difference.
†SDD was as follows: lansoprazole, 30 mg; omeprazole, 40 mg; pantoprazole, 40 mg; rabeprazole sodium, 40 mg; ranitidine hydrochloride, 300 mg; cimetidine, 800 mg; famotidine, 40 mg; cisapride, 40 mg; domperidone, 40 mg; metoclopramide hydrochloride, 40 mg; antacid, 2 g.

**Figure 5.** Patient satisfaction in the test-and-treat group (n=124) and the endoscopy group (n=120).
benefit of anti–H pylori treatment has been demonstrated unequivocally only in patients with PUD, we aimed to prevent any bias by a possible effect in patients with functional dyspepsia or GERD. Inevitably, our study had some drawbacks. Patients were recruited by their own GPs, which may have introduced a potential selection bias, limiting the comparability between the study patients and the normal dyspeptic population. Moreover, our study does not allow a comparison of the test-and-treat strategy with the currently most often used approach (empirical treatment). We chose to include a control group (prompt endoscopy) rather than an empirical study group, to determine whether the test-and-treat strategy missed any important disease.

We assumed that the abnormalities present in the test-and-treat group at inclusion were similar to the endoscopic findings in the prompt endoscopy group. It should be noted that, in the patients in the test-and-treat group who underwent endoscopy, H pylori–positive PUD was not diagnosed. This strongly indicates that the test-and-treat strategy correctly identified all patients with H pylori–associated PUD and that these patients received adequate treatment. The only patient in the test-and-treat group in whom PUD was diagnosed had erosive inflammation in the duodenal bulb at 6 months after anti–H pylori treatment. Endoscopic biopsies excluded H pylori infection. Nonsteroidal anti-inflammatory drugs were not prescribed to this patient during the study year, but over-the-counter use cannot be excluded.

The efficacy of the anti–H pylori regimen was greater than 85% in both study arms. Susceptibility testing before anti–H pylori treatment did not seem to improve the treatment success rate, but this may be related to the low prevalence of clarithromycin resistance in our region. An often-cited argument against the test-and-treat strategy is the possibility of overlooking gastric or esophageal cancer. In our study, gastric cancer was diagnosed in 1 patient 3 weeks after inclusion, which is a duration of delay that has been suggested to be acceptable.26

Proton pump inhibitors were more often prescribed in the endoscopy group than in the test-and-treat group. This was most likely related to the prescription of PPIs in nearly all patients with endoscopy-proved GERD, as recommended by the study guidelines, whereas in primary care it is common practice to start treatment with a histamine2-receptor antagonist if GERD is expected but not proved. Prokinetics were more often prescribed in the test-and-treat group, which was clearly the direct result of our study protocol advising use of prokinetics in all noninvasively tested H pylori–negative patients. Other dyspepsia-related drugs were used equally often in both study groups. Patients in the test-and-treat group more often consulted their GPs for dyspepsia, which may indicate more effective treatment or better reassurance in the endoscopy group. The use of other medical resources, including specialist referrals, hospital admissions, and additional investigations for dyspepsia other than endoscopy, were comparable in both study groups.

Most current guidelines advocate empirical treatment with acid-suppressive agents as a first approach to dyspepsia. Whether the test-and-treat strategy is more cost-effective than an empirical approach cannot be concluded from this study. One of the most important variables influencing cost-effectiveness of any approach for dyspepsia, however, is the number (and cost) of endoscopies.8,10 The study by Bytzer et al9 comparing an empirical acid-suppressive approach with histamine2-receptor antagonist with prompt endoscopy, showed a 34% reduction in the number of endoscopies in the first year. When compared with this outcome, both our study and the study by Lassen et al13 showed a higher reduction in number of endoscopies (67.4% and 60%, respectively). It could therefore be hypothesized that the test-and-treat approach may be more cost-effective than empirical acid suppression. It should be emphasized, however, that the cost-effectiveness of a test-and-treat strategy largely depends on the prevalence of PUD and H pylori infection in the population. The reported declining prevalence of H pylori infection has a negative impact on the predictive value of noninvasive tests for H pylori. Moreover, the decreasing prevalence of PUD will limit the number of patients most clearly benefiting from anti–H pylori treatment.

In conclusion, a test-and-treat approach for dyspeptic patients in primary care is as effective and safe as a strategy in which all patients are immediately referred for endoscopy. Only a minority (33%) of patients are referred for endoscopy after test-and-treat.

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Corresponding author and reprints: Jacob C. Thijs, MD, PhD, Bethesda Hospital, Dr G. H. Amshoffweg 1, 7909 AA Hoogeveen, the Netherlands (e-mail: n.l.a.arents@mmb.aug.nl).

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