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Treatment of *H. pylori* Infection: The Reality

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Despite the wide dissemination of information on *Helicobacter pylori*, there is still a great deal of variation in how general practitioners treat the infection and in which circumstances they prescribe eradication therapy for *H. pylori*. Specialty societies have developed consensus guidelines that recommend a strategy to test and treat dyspeptic patients for *H. pylori* infection although the data to support these recommendations are weak at the present time. As a result, there is still confusion about the indications for treatment and the treatment regimens that are likely to be effective in routine clinical practice.

INTRODUCTION

There are compelling data to suggest that treatment of *Helicobacter pylori* infection in patients with duodenal ulcer disease is associated with an improvement in health outcomes and a reduction in disease management costs. Despite the data, there is a great deal of confusion about therapy, and surveys of primary care physicians suggest that significant numbers of patients receive inadequate therapy. The challenge, therefore, is to translate results obtained in randomized controlled trials (efficacy data) into results obtained in routine clinical practice (effectiveness data).

PRIMARY CARE PHYSICIANS AND *H. PYLORI* INFECTION

The attitudes of primary care physicians to the treatment of *H. pylori* infection have been examined in several studies. In one study conducted in a family practice in 1995, Penston and Mistry studied 154 patients treated for *H. pylori* infection [1]. Eighty percent were treated for duodenal ulcer and the remainder for non-ulcer dyspepsia or reflux disease. They found that *H. pylori* infection was documented in only a third of patients prior to the initiation of therapy. The vast majority of these patients were, therefore, receiving empirical therapy in the absence of documented infection. Furthermore, when they examined the regimens being prescribed, they found that 56 different treatment regimens had been prescribed, and the most frequently prescribed regimen was omeprazole and amoxicillin, a poor regimen for the eradication of *H. pylori*. The management of patients with complicated ulcer disease was particularly poor and did not assure against future hemorrhage or perforation. In a more recent study, Breuer et al. reported a survey of 486 family practitioners who filled out a questionnaire [2]. Eighty-nine percent of them reported that they treated patients for *H. pylori* infection at first presentation with ulcer disease. Sixty-five percent treated all *H. pylori*-infected patients regardless of the clinical circumstances, and 72 percent treated patients with non-ulcer dyspepsia. These data were significantly different from gastroenterologists, 98 percent of whom treated patients with ulcer disease while only 43 percent treated non-ulcer dyspepsia and 24 percent treated all *H. pylori*-positive cases regardless of clinical circumstances.

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Dyspepsia and peptic ulcer disease

Dyspepsia is defined as a persistent or recurrent abdominal pain centered in the upper abdomen. Dyspepsia is a common finding in clinical practice, but symptoms have a poor predictive value for the underlying diagnosis [3]. Approximately half of the patients presenting to primary care doctors with dyspepsia have a functional disorder, and only 15 percent of them have peptic ulcer disease. Unfortunately, this is not as well appreciated in primary care as it should be. In a recent survey of primary care physicians, we found that 48 percent of them believed that symptoms of ulcer disease were strongly correlated with the endoscopic diagnosis [4]. A number of studies on *H. pylori* eradication in non-ulcer dyspepsia have been published, and all have been criticized for their methodology [5]. At the present time, it appears that only a minority of patients with non-ulcer dyspepsia will benefit from therapy directed at *H. pylori* infection.

In 1985, the American College of Physicians published a guideline on dyspepsia which suggested that patients should be given an empirical trial of H_2 receptor antagonists and undergo further testing only if symptoms relapsed or if they persisted despite therapy. [6]. These guidelines have been widely used by managed care organizations to determine which patients should undergo endoscopy but were never systematically analyzed until 1996. Bytzer et al. [7] randomized patients to treatment with H_2 receptor antagonists, as recommended by the American College of Physicians, or early endoscopy and followed the patients for a year thereafter. Patients were cared for by primary care physicians who determined if endoscopy or further interventions should be performed. At the end of one year, patient satisfaction was poorer, drug costs were higher and the time lost from work was higher in the group of patients randomized to initial H_2 receptor antagonist therapy. A large percentage of the patients initially randomized to H_2 receptor antagonist therapy eventually had endoscopy for recurrent or unresolved symptoms. This study and the discovery of *H. pylori* infection have rendered these guidelines obsolete. It is not surprising, given the poor results with this guideline that it has had a limited impact on routine clinical practice.

In 1996, the European *H. pylori* study group issued guidelines on the management of dyspeptic patients and suggested that patients 45 years or younger should be tested and treated for *H. pylori* using a non-invasive test. It was suggested that older patients or patients with so-called alarm symptoms (bleeding, weight loss, early satiety) should undergo investigation because of the small but increased risk of missing a gastric malignancy in these subjects [9]. These guidelines are consensus based and cannot claim to have met the criteria for an evidence-based approach. Economic models suggest that serologic testing and treatment become cost-effective as an initial strategy when as few as 15 percent of patients are cured of their symptoms. Preliminary data from our group suggest that complete cure of all symptoms that is sustained for one year may be possible in a substantial number of infected patients, supporting the position of these consensus statements [10].

H. pylori infection has been associated with gastric cancer in several epidemiological studies. A recent economic model suggested that it might be cost-effective to test and treat patients for *H. pylori* infection to prevent gastric cancer [11]. Preliminary data from patients with early gastric cancer in Japan suggest that when *H. pylori* infection is eradicated, there is a significant reduction in the rate of new gastric cancers that develop at other sites in the stomach [12]. There are no data upon which a clear recommendation may be made at the present time.

TREATMENT REGIMENS

1. FDA approved regimens

There are three dual drug regimens in the United States, and all have similar eradication rates:

Omeprazole and clarithromycin. The eradication rate with this regimen was 78 percent in U.S. trials and 82 percent in European trials [13, 14]. Compliance has generally been good, and the regimen is generally well tolerated. The principal side-effect is taste perversion due to clarithromycin.

Ranitidine bismuth citrate and clarithromycin. Ranitidine bismuth citrate is a new compound that is a highly soluble form of bismuth. An eradication rate of 82 percent was reported in the United States [4]. Higher eradication rates have been reported in European studies.

There is only one study that compares two dual therapies in a randomized trial. In this study, eradication rates were lower than in other reports and were significantly better for the combination of ranitidine bismuth citrate with clarithromycin (73 percent) compared to omeprazole with clarithromycin (53 percent) [15].

Bismuth-based triple therapy. Bismuth-based triple therapy consists of a combination of bismuth, metronidazole and tetracycline. Amoxicillin has been used instead of tetracycline with poorer results. The three drugs are generally co-prescribed with an anti-secretory drug (H_2 receptor antagonist or proton pump inhibitor) in patients with peptic ulcer disease. With this regimen, 16-18 pills need to be taken every day, which affects compliance. Eradication rates as high as 95 percent have been reported in some studies, but the overall eradication rate is probably lower in U.S. studies and averages 82 percent.

2. Other regimens: short triple therapies

To decrease cost and enhance compliance, shorter periods of therapy have been tried with a variety of agents, administered twice a day. These regimens are generally simpler to take, and lower doses of some drugs reduce side-effects.

Proton pump inhibitor based triple therapies. Proton pump inhibitors (lansoprazole, omeprazole) used in combination with two antibiotics are a major advance in the therapy of *H. pylori* infection. Two large European trials have shown a high degree of efficacy [17, 18]. Seven, 10 and 14-day therapy have been reported to yield similar results in European studies, but in the United States, a decrease in efficacy has been reported with seven-day therapy, and at the current time, 10-day therapy is preferred by some experts [19]. As all drugs are given twice a day, compliance is enhanced. The best results are with combinations of a proton pump inhibitor, amoxicillin and clarithromycin or the combination of a proton pump inhibitor with metronidazole and clarithromycin.

Ranitidine bismuth citrate triple therapy. Data from Europe and the United States have shown high eradication rates with ranitidine bismuth citrate in combination with amoxicillin and clarithromycin or metronidazole and clarithromycin. High eradication rates have also been reported with a combination of ranitidine bismuth citrate and metronidazole and clarithromycin in Europe [20]. In the United States, an eradication rate of 95 percent was reported for the combination of ranitidine bismuth citrate with amoxicillin and clarithromycin and 87 percent for ranitidine bismuth citrate with metronidazole and tetracycline [21].

PROBLEMS WITH THERAPY IN THE COMMUNITY

While controlled trials provide a measure of efficacy with a given regimen, the results do not necessarily translate into routine clinical practice. The principal problems in routine practice are compliance and resistance [22, 23].

Compliance

Compliance with therapy is an important variable that affects results with all of the treatment regimens. Compliance is a particular problem with bismuth-based triple therapy because of the number and frequency of the pills that need to be taken and the relatively high incidence of minor side-effects. Decreased compliance is associated with a decrease in eradication rates. A blister pack of each day's medication has been developed for bismuth-based triple therapy, but it is considerably more expensive than the cost of the drugs bought individually.

Resistance

Primary resistance to metronidazole is an important problem in some populations. Resistance rates from 24 to 70 percent have been reported in the United States, and eradication rates with metronidazole-containing regimens are decreased when resistance is present [24]. A recent study found much higher prevalence rates of metronidazole resistance (47 to 66 percent) throughout the United States [25]. Clarithromycin resistance rates have been increasing with time in the United States, from three to four percent in 1994 to approximately 13 percent in 1996 [26]. Clarithromycin resistance is associated with a decreased efficacy with clarithromycin containing regimens.

EFFECTIVENESS OF THERAPY IN ROUTINE CLINICAL PRACTICE

In a community-based study of gastroenterologists, Fennerty et al. [27] showed that the combination of metronidazole, omeprazole and clarithromycin had an eradication rate of 92 percent, while omeprazole and clarithromycin dual drug therapy had an eradication rate of 76 percent, and bismuth based triple therapy had an eradication rate of 73 percent. Data on eradication rates in the community with primary care providers providing therapy are still lacking. A recent study suggests that only 39 percent of patients with peptic ulcer disease were tested for *H. pylori*, and of these, only half received treatment with antimicrobials [28].

COST-EFFECTIVENESS MODELS OF DIFFERENT REGIMENS

Computer models that estimate the cost of therapy with several of the regimens have been developed. Vakil et al. compared four treatment regimens for the eradication of *H. pylori* and demonstrated that a strategy to eradicate *H. pylori* was considerably less expensive than traditional H_2 receptor antagonist therapy even if the cost of the H_2 receptor antagonist was decreased to $1 for the entire year of maintenance of therapy [29]. This is because the principal determinant of cost with *H. pylori* eradication therapy is the cost of recurrence. Regimens with high eradication rates are cost-effective regardless of the initial cost of the drug therapy [18]. This model is relevant to the managed care environment because costs were assessed over a two-year time frame. In another model based on actual eradication results in a community-based trial (effectiveness data), we found that the expected costs with proton pump inhibitor based triple therapy were lower than with two drug therapies [30]. The new short triple drug therapies should replace dual drug therapies as the treatment of choice for *H. pylori* infection.

In summary, despite significant advances in our understanding of the pathogenesis and treatment of *H. pylori* related infection, treatment of patients in the community is incomplete and inadequate.

REFERENCES

1. Penston, J.G. and Mistry, K.R. Eradication of *Helicobacter pylori* in general practice. Aliment. Pharmacol. Ther. 10:139-145, 1996.
2. Breuer, T., Malaty, H., Goodman, K., Sudhop, T., and Graham, D.Y. Does disease presentation influence treatment of *H. pylori* infection. Gut 39:A21, 1996.
3 Johnsen, R., Bernersen, B., Straume, B., Forde, O., Bostad, L., and Burhol, P. Prevalences of endoscopic and histological findings in subjects with and without dyspepsia. Br. Med. J. 302:749-752, 1991.
4. Vakil, N. and McCall, T. Changes in primary care approaches to *H. pylori* diagnosis and treatment in 1996. Gastroenterology 112:A219, 1997.
5. Talley, N.J. A critique of therapeutic trials in *Helicobacter pylori*-positive functional dyspepsia. Gastroenterology 106:1174-1183, 1994.
6. Health and Public Policy Committee, American College of Physicians. Endoscopy in the evaluation of dyspepsia. Ann. Intern. Med. 102:266-269, 1985.
7. Bytzer, P., Hansen, J., and de Muckadell, O. Empirical H2 blocker therapy or prompt endoscopy in management of dyspepsia. Lancet 343:811-815, 1994.
8. Schwartz, L.K., Woloshin. S, and Welch, G. Trends in diagnostic testing following a national guideline for evaluation of Dyspepsia. Arch. Intern. Med 156:873, 1996.
9. European *Helicobacter pylori* study group. Current European concepts on the management of *Helicobacter pylori* infection. The Maastricht Consensus Report, 1996.
10. Vakil, N. and Puetz, T. One year outcome of a test and treat strategy for *H. pylori* infection in dyspeptic patients. Gastroenterology 112:A319, 1997.
11. Parsonnet, J., Harris, R., Hack, H., and Owens, D. Modelling cost-effectiveness of *Helicobacter pylori* screening to prevent gastric cancer: a mandate for clinical trials. Lancet 348:150-154, 1996.
12. Uemura, N., Mukai, T., Okamoto, S., Yamaguchi, S., Mashiba, H., Taniyama, K., Sasaki, N., Haruma, K., Surnii, K., and Kajiyama, G. *Helicobacter pylori* eradication inhibits the growth of intestinal type of gastric cancer in initial stage. Gastroenterology 110:A282, 1996.
13. Logan, R., Bardhan, K., Celestin, L., Theodossi, A., Palmer, K., Reed, P., Barum, J., and Misiewicz, J.J. Eradication of *H. pylori* and prevention of recurrence of duodenal ulcer: a randomized, double-blind, multicentre trial of Omeprazole with and without clarithromycin. Aliment. Pharmacol. Ther. 9:417-423, 1995.
14. Hunt, R., Schwartz, H., Fitch, D., Fedorak, R., Alkawas, F., and Vakil, N. Dual therapy of clarithromycin and Omeprazole for treatment of duodenal ulcers associated with *H. pylori* infection. Gut 37(suppl 1):A5, 1995.
15. Pare, P., Romaozinho, J., Bardhan, K., French, P., and Roberts, P.M. Ranitidine bismuth citrate (RBC) is more effective than omeprazole in the eradication of *H. pylori* when co-prescribed with clarithromycin. Gastroenterology 112:A251, 1997.
16. Cutler, A.F. and Schubert, T.T. Patient factors affecting *H. pylori* eradication with triple therapy. Am. J. Gastroenterol. 88:505-509, 1993.
17. Lind, T., van Zanten, V., and Unge, P. Eradication of *Helicobacter pylori* using one week triple therapies combining Omeprazole with 2 antimicrobials. Helicobacter 1:138-144, 1996.
18. Misiewicz, J., Harris, A., Bardhan, K., Levi, S., and Langworthy, H. One week low-dose triple therapy for eradication of *H. pylori*: a large multicentre, randomized trial. Gut 38 (suppl 1):Al, 1996.
19. Laine, L., Frantz, J., Baker, A., and Neil, G. Randomized comparison of dual therapies and PPI-based triple therapies for *H. pylori* infection. Gastroenterology 112:A192, 1997.
20. Bardhan, K.D., Wurzer, H., Marcelino, M., Jahnsen, J., and Lotay, N. High cure rates with ranitidine bismuth citrate plus clarithromycin given twice daily. Gut 39(suppl 2):A36.
21. Laine, L., Estrada, R., Trujillo, M., and Emami, S. Randomized comparison of ranitidine bismuth citrate (RBC) based triple therapies for *H. pylori*. Gastroenterology 112:A192, 1997.
22. Graham, D.Y., Lew, G.M., Malaty, H.M., Evans, D.G., Evans, D.J., Klein, P.D., Alpert, L.C., and Genta, R.M. Factors influencing the eradication of *Helicobacter pylori* with triple therapy. Gastroenterology 102:493-496, 1992.

23. Bell, G.D., Powell, K., Burridge, S., Palleceros, A., Jones, P.H., Gant, P., Harrison, G., and Trowell, J.E. Experience with triple anti-*Helicobacter pylori* eradication therapy: side-effects and the importance of testing the pre-treatment bacterial isolate for metronidazole resistance. Aliment. Pharmacol. Ther. 6:427-435, 1992.
24. McNulty, C.A. and Dent, J.C. Suceptibility of clinical isolates of *Campylobacter pylori* to twenty-one anti-microbial agents. Eur. J. Clin. Microbiol. Infect. Dis. 7:566, 1988.
25. Weissfeld, A., Haber, M., Rose, P., Kidd, S., and Siepman, N. Geographical distribution in the United States of primary resistance to clarithromycin and metronidazole in patients infected with *H. pylori*. Gastroenterology 112:1328, 1997.
26. Vakil, N., McSorley, D., Hahn, B., Ciocola, A., and Webb, D. Clarithromycin-resistant *Helicobacter pylori* in the United States. Gastroenterology 112:A318, 1997.
27. Fennerty, M.B., Lieberman, D.L., Magaret, N. and the GORGE Consortium. Effectiveness of *H. pylori* treatment regimens in clinical practice: A community-based outcome study Gastroenterology 112:A14, 1997.
28. Roll, J., Weng, A., and Newman, J. Diagnosis and treatment of *Helicobacter pylori* infection among California Medicare patients. Arch. Intern. Med. 157:994-998, 1997.
29. Vakil, N. and Fennerty, M.B. Economic modeling of medical therapy for *H. pylori*-related peptic ulcer disease. Am. J. Gastroenterol. 91:239-245, 1996.
30. Vakil, N. and Fennerty, B. Cost-effectiveness of treatment regimens for *H. pylori* infection based on a community practice effectiveness study. Gastroenterology 112:A47, 1997.