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Do Primary Care Physicians Underprescribe Antibiotics for Peptic Ulcer Disease?

Report from an Italian Research Network

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■ OBJECTIVE To determine how often primary care physicians prescribe eradication therapy for peptic ulcer disease (PUD) and nonulcer dyspepsia (NUD).

■ STUDY DESIGN During a 2-year period (1998–2000) we analyzed data concerning patients with PUD or NUD seen by 80 Italian primary care physicians uniformly distributed throughout the country. We classified patients as having a definitive or presumptive diagnosis on the basis of the completeness of the diagnostic workup and interpreted the prescription of antibiotics for dyspepsia as evidence of attempted eradication of *Helicobacter pylori*.

■ POPULATION Consecutive ambulatory patients.

■ OUTCOME MEASURED The frequency with which predefined groups of patients received eradication therapy.

■ RESULTS Of 6866 patients, 690 (10%) received eradication therapy. Of 2162 patients with PUD, 596 (27.6%) received eradication therapy; of 4704 patients with NUD, however, only 94 (2%) received this treatment ($P = .0001$). A total of 341 (37.7%) of 904 PUD patients with a definitive diagnosis were given eradication therapy and 255 (20.3%) of 1258 PUD patients with a presumptive diagnosis were given therapy ($P < .0001$). In NUD patients, 7 of 743 (0.9%) with a definitive diagnosis received eradication therapy, while 87 (2.2%) of 3961 of those with a presumptive diagnosis received the same therapy ($P = 0.025$).

■ CONCLUSIONS While Italian primary care physicians appropriately target eradication therapy for *H pylori* infection in patients with peptic ulcer disease rather than nonulcer disease, the intervention was still underused in these patients. Improvements in this prescribing behavior are needed.

■ KEY WORDS *Helicobacter pylori*; peptic ulcer; family physicians; eradication therapy [non-MeSH]; computer database [non-MeSH). (*J Fam Pract 2002; 51:265*)

Data from the medical literature[1-3] and from 2 ad hoc international consensus conferences[4,5] suggest that antibiotic therapy aimed at eradication of *Helicobacter pylori* causes persistent healing of peptic ulcer and should therefore be the treatment of choice for patients with peptic ulcer disease (PUD). While administering eradication therapy to *H pylori*–positive patients with nonulcer dyspepsia (NUD) remains under debate,[6,7] such therapy is generally not recommended.

How these findings are used in clinical practice is largely unknown. Two surveys have reported rates of eradication therapy given by primary care physicians (PCPs) of close to 90% in PUD patients and 50% in NUD patients.[8,9] This information is strongly biased, however, in fact that it was derived from answers to specific questions asked by mail. Responses indicate treatment under ideal conditions rather than real ones. To our knowledge, no reliable analysis on this subject is available.

Our work evaluated the frequency with which eradication therapy was administered in Italy to dyspeptic patients with and without PUD from September 1998 to September 2000. We assessed whether the performance of a complete diagnostic workup affected the rate at which eradication therapy was prescribed. We also evaluated the combination therapies that physicians used.

METHODS

The study population included 7336 patients with a PCP's diagnosis of PUD or NUD from September 1998 to September 2000. A total of 470 (6.4%) of these patients were referred to a gastroenterologist

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and excluded, leaving a final study population of 6866 patients.

Selection of Physicians and Data Collection

In 1994, software designed by a team of epidemiologists and computer experts from Tor Vergata University, Rome, Italy, was given to 19,000 Italian PCPs. The software was designed to help physicians collect data from their patients during each visit.[10] Data on the number of visits to PCPs during 1993 were obtained. One year later, 2000 physicians agreed to compare the percentage of patients included in their database with the total number of visits and to return their accumulated databases for quality control.

Among the 371 physicians with a quality database of good quality (defined as including at least 95% of their patients in the database and declaring a similar number of patients as in the previous year, 1993), 120 agreed to participate in our study. New software was designed to gather data concerning the performance of eradication therapy for *H pylori* in the past, the requests and results of upper gastrointestinal endoscopy and abdominal sonography, and the prescribed treatment. The diagnosis was required in the database (ie, it was not possible to have access to subsequent fields in the absence of these data). Furthermore, the software was able to recognize the pharmacologic class of each drug from its generic name. Regarding antibiotic prescriptions for patients in whom a diagnosis of PUD or NUD had been made, the physician was asked if the treatment was intended for the diagnosed disease or for unrelated conditions.

From the start of the study, physicians were asked to include in the new database all patients coming to the office for an initial visit to evaluate dyspepsia of at least 3 months' duration. If new data concerning diagnostic procedures or treatment emerged during subsequent visits, these were added to the database. It was possible for the PCP to change the diagnosis on the basis of new findings. The diagnosis made during the last visit was considered the final diagnosis.

Although participating PCPs knew they were involved in a study concerning their behavior in treating dyspepsia, they did not know the study's goal: to determine the rate at which they had prescribed eradication therapy to dyspeptic patients. Physicians were given personal computers as an incentive to participate in the study.

All computers were linked to a central server, located in the epidemiology laboratory of Tor Vergata University of Rome, to which all data were transferred weekly. Each patient was identified by a code number assigned by the attending physician.

The physicians who agreed to participate in the study were stratified according to the following geographic criteria. Approximately one half were in the north of Italy and the other half were in the south. Within each of these areas, approximately one half of participating PCPs worked in cities with 100,000 inhabitants or fewer and the other half in towns with more than 100,000 inhabitants. Forty PCPs were randomly excluded from the study to avoid overrepresentation of certain areas of the country, particularly large cities. Therefore, the data in our study refer to a total of 80 PCPs. The age range of participating physicians was 32 years to 63 years; 61 were men; and all had been practicing PCPs for at least 5 years (range: 5 years to 36 years). Eight PCPs were specialists: 6 in internal medicine, 1 in gynecology, and 1 in rheumatology.

A definitive diagnosis of peptic ulcer was based on findings obtained by the reference standard examination (upper gastrointestinal endoscopy for the definitive diagnosis of PUD) or by a combination of findings (a definitive diagnosis of NUD required normal findings at upper gastrointestinal endoscopy and abdominal sonography). In the other cases, the diagnosis was considered presumptive.

Therapy

We considered the combination therapies most frequently evaluated in clinical trials: bismuth-based triple therapy (bismuth plus metronidazole and tetracycline; bismuth plus clarithromycin and tetracycline; bismuth plus clarithromycin and amoxicillin; bismuth plus metronidazole and amoxicillin[11,12]); proton pump inhibitor (PPI)–based triple therapy (PPI plus 2 of the following: amoxicillin, clarithromycin, or metronidazole[13]); PPI-based dual therapy (PPI plus amoxicillin or clarithromycin or metronidazole[14]); and others (none of the former).

Statistical Analysis

The chi-squared test was used to compare the frequency of discrete variables. A P value of less than .05 was required for statistical signifi-

TABLE 1

FREQUENCY OF ERADICATION THERAPY OF *HELICOBACTER PYLORI*

Diagnosis	Eradication Therapy No. (%)	No Eradication Therapy No. (%)
Peptic ulcer disease (n = 2162)	596* (27.6)	1566 (72.4)
Nonulcer dyspepsia (n = 4704)	94* (2)	4610 (98)

* $P = .0001$.

cance. Statistical Package for the Social Sciences software was used for the evaluation of significance.

RESULTS

PUD was diagnosed in 2162 patients (1412 men, average age = 45 ± 15.8 years). NUD was diagnosed in 4704 patients (1328 men, average age = 42 ± 13.2 years). Among the 2162 patients with PUD, eradication therapy was prescribed for 481. However, since 115 of the 2162 patients had received such therapy before entering the study, the total number of patients who received antibiotic therapy was 596 (27.6%). Other treatments (mostly H_2-receptor antagonists or PPIs) were prescribed to the remaining 1566 patients with PUD.

Eradication therapy was given to 94 (2%) of 4704 patients diagnosed with NUD (17 patients had received treatment before 1998). Table 1 shows that eradication therapy was prescribed more frequently for patients with PUD than for those with NUD (27.6% vs 2%; $P = .0001$).

Among patients with PUD, eradication therapy was prescribed more frequently for those with a definitive diagnosis than for those with a presumptive diagnosis (37.7% vs 20.3%, respectively; $P < .0001$), but the reverse was observed in NUD patients (0.9% vs 2.2%; $P = .025$) (Table 2). The latter difference is of uncertain clinical significance.

Of 904 patients with a definitive diagnosis of PUD, 223 had a newly diagnosed peptic ulcer; 97 (43.5%) of these were treated with eradication therapy. We observed no change in the percentage of patients with PUD receiving eradication therapy during the study period: 220 of 1005 (22%) during the first year and 261 out of 1157 (22.6%) during the second year.

Of the 80 PCPs, 72 prescribed some kind of eradication therapy. Seven of the 8 physicians who had never prescribed eradication therapy were living in small towns in the south of Italy. Other characteristics of the nonprescribers, such as age and sex, were similar to those of the remaining physicians.

Of 690 patients who received eradication therapy, the type of combination was known for 558. The combination regimen used for the 132 patients treated before the study began was not available. Of 558 patients, 301 (54%) were given PPI-based dual therapy and 225 (40.3%) received PPI-based triple therapy. Other treatments were prescribed to 32 (5.7%) patients (Table 3).

Among patients in whom dual therapy was prescribed, PPI plus clarithromycin was used in 242 patients (43.4% of the total population of treated patients; 80.4% of the subgroup receiving dual therapy). The combination of PPI, clarithromycin, and metronidazole was the most widely used treatment in patients who received triple therapy: it was prescribed to 192 patients (34.4% of all treated patients; 85.3% of the subgroup given PPI-based triple therapy).

TABLE 2
FREQUENCY OF ATTEMPTED ERADICATION BY DEFINITIVE OR PRESUMPTIVE DIAGNOSIS

Diagnosis	Attempted Eradication (%)	Other Therapies (%)
Peptic ulcer disease		
Definitive (n = 904)	341 (37.7)*	563 (62.3)
Presumptive (n = 1258)	255 (20.3)*	1003 (79.7)
Nonulcer dyspepsia		
Definitive (n = 743)	7 (0.9) †	736 (99.1)
Presumptive (n = 3761)	87 (2.2) †	3684 (97.8)

*$P < .0001$.
†$P < .025$.

Most patients for whom other therapies were prescribed received bismuth-containing combinations. A combination of bismuth and PPI was prescribed to 10 patients (1.8% of the total population). The drug was added to PPI-based triple therapy in 10 patients (1.8% of the total population) and to PPI-based dual therapy in 2 patients (0.4% of the total population). The remaining 10 patients were treated as follows: a combination of 2 antibiotics without PPI (2 patients), H_2-based triple therapy (6 patients), or antibiotic monotherapy (2 patients). None of these combinations is known to eradicate *H pylori* effectively.

DISCUSSION

The data from our study indicate that from 1998 to 2000, the majority of patients with PUD seen by the PCPs participating in the study were not treated with antibiotic therapy aimed at the eradication of *H pylori*.

In our series, only approximately one third of patients with a definitive diagnosis of PUD were treated with antibiotic therapy, a figure much lower than the 90% reported in nationwide surveys during 1995 and 1996 in the United States and Germany.[8,9] We believe that the most important factor underlying this difference may be the study design. Our study was based on the actual treatment given by the physicians to their patients; previous studies, however, were based on responses to a mailed questionnaire. While the previous studies may reflect ways in which PCPs would ideally treat their patients, some discrepancy is unavoidable when passing from theory to practice.

Other studies based on real-world prescription data had results similar to ours, despite having a small sample size[15,16] or studying underserved populations.[17,18] In light of these data, we suspect that the underuse of antibiotic therapy for PUD disease is common in many areas of the Western world.

TABLE 3

ERADICATION REGIMENS USED BY ITALIAN PRIMARY CARE PHYSICIANS

Eradication Regimen	Patients: No. (%)
Dual therapy	301 (54)
PPI + C	242 (43.4)
PPI + A	42 (7.5)
PPI + M	17 (3.1)
Triple Therapy	225 (40.3)
PPI + C + M	192 (34.4)
PPI + C + A	10 (3.6)
PPI + A + M	13 (2.3)
Other	32 (5.7)

A denotes amoxicillin; C, clarithromycin; M, metronidazole;PPI, proton pump inhibitor.

Since PCPs were not required to include information on *H pylori* testing in the database, we did not have reliable data on the frequency of testing or on the relative frequency of positive and negative results. Therefore, it is possible that the low number of prescriptions of eradication therapy for patients with PUD was caused by a high rate of *H pylori*–negative peptic ulcer. This seems improbable, however, since a high rate of *H pylori*–positive peptic ulcers has been reported in Italian patients.[19]

One likely reason for the low prescription rate of eradication therapy by PCPs was concern about patient compliance and the side effects of antibiotics. Although a recent study reported discontinuation of therapy because of adverse events or noncompliance in less than 10% of patients,[7] it is well known that data on compliance coming from research studies are not automatically transferable to clinical practice.[20]

Since eradication therapy was prescribed by the majority of PCPs involved in our study, our findings suggest that an awareness of new information does not necessarily effect changes in physicians' prescribing patterns.[21-23] Both knowledge-oriented strategies (ie, purely educational interventions) and behavior-oriented interventions (ie, strategies intended to alter behavior, usually by incentives and penalties) are necessary to change physicians' prescribing patterns regarding PUD. Furthermore, change strategies should be matched to the type of clinician. Our data suggests that most PCPs involved in our study are pragmatists.[24] These physicians will not change their behavior in a way that would increase their workload or conflict with patient expectations. Therefore, to increase the rate of prescriptions of eradication therapy for PUD, it is crucial to remove obstacles (eg, facilitate the performance of *H pylori* testing and endoscopy) and to focus educational interventions on practical issues (eg, place emphasis on the fact that prescribing eradication therapy to these patients may lead to a reduction of visits in the future).

The very low rate of eradication therapy (less than 3%) for patients with NUD in our study seems at odds with the high prevalence (more than 50%) of eradication therapy prescribed by US physicians for patients with NUD.[9] The same factors explaining the different rates of eradication therapy for patients with PUD apply to differing rates in patients with NUD.

Interestingly, antibiotic therapy was prescribed at a significantly lower rate for NUD patients with a definitive diagnosis. This fact suggests that physicians did not expect important benefits from *H pylori* eradication in patients who did not have gastroduodenal lesions. Another important finding was that most treated patients received less than optimal treatment. The majority of patients receiving eradication therapy were given a regimen consisting of no more than 2 drugs although this regimen is less effective[25] and less convenient from a cost–benefit perspective than is a 3-drug combination.[26,27] Our findings are strikingly similar to those of a small study performed in Scotland[28] that showed that more than 55% of patients receiving eradication therapy were treated with PPI-based dual therapy. These data suggest that PCPs are choosing their prescribing options in relation to short-term cost minimization rather than long-term cost effectiveness.

Generalizing our data to the entire Italian health care system may not be valid. Although much attention was paid to the reliability of collected data and to creating a wide geographic distribution of physicians involved in the study, stringent criteria were used for inclusion: ownership of a personal computer, capability of using fairly complex software, and willingness to participate. The majority of Italian PCPs do not share these characteristics. This hypothesis is demonstrated by the fact that only 80 physicians were selected from the initial pool of 19,000. There is no reason, however, to suggest that the above-mentioned characteristics interfere with changing clinicians' practice patterns.

CONCLUSIONS

Our study shows that recommendations for eradication therapy for PUD did not translate into clinical practice in Italy until at least 2000. This means that Italian PCPs failed to reap the clinical and financial benefits resulting from this treatment. This finding, in conjunction with the administration of suboptimal eradication therapy to treated patients, indicates the need for both educational efforts and behavior-oriented interventions aimed at causing the prescribing patterns of eradication therapy of Italian PCPs to conform to the standard reported in the literature.

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