The dyspepsia alphabet: DU, GU, GERD, NERD, NUD/FD and UD

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ABR Thomson. The dyspepsia alphabet: DU, GU, GERD, NERD, NUD/FD and UD. Can J Gastroenterol 2000;15(1): 49-55. The care of patients with dyspepsia may be almost as confusing as the many terms that are used to describe this very common symptom. A symptom-based approach may prove to be ideal for the patient with undiagnosed dyspepsia. This brief overview describes some of the many terms used to describe dyspepsia. Clearly, new treatment algorithms are needed for the care of patients with undiagnosed dyspepsia seen in a primary care setting.

Key Words: *Duodenal ulcer; Functional dyspepsia; Gastric ulcer; Gastroesophageal reflux disease; Nonulcer dyspepsia; Normal endoscopy reflux disease; Uninvestigated dyspepsia*

L'alphabet de la dyspepsie : DU, GU, GERD, NERD, NUD/FD, UD

RÉSUMÉ : Le traitement des patients atteints de dyspepsie est presque aussi difficile à circonscrire que les nombreux termes qui décrivent ce trouble très fréquent. Une approche fondée sur les symptômes peut s'avérer idéale pour les patients souffrant de dyspepsie non diagnostiquée. Voici un bref aperçu des termes utilisés pour décrire la dyspepsie. De toute évidence, de nouveaux algorithmes de traitement s'imposent pour la prise en charge des patients souffrant de dyspepsie non diagnostiquée dans les milieux de soins primaires.

A DIFFICULT MATTER OF DEFINITION

Dyspepsia has been defined as upper abdominal pain or discomfort (1; and Talley et al, unpublished data), but may also be associated with bloating, distention, nausea or vomiting (2,3). Retrosternal burning (heartburn) and acid regurgitation may be associated with other dyspeptic symptoms, but when these symptoms are predominant, gastroesophageal reflux disease (GERD) is diagnosed. However, functional dyspepsia (FD), also known as nonulcer dyspepsia (NUD), may occur with heartburn and regurgitation as nonpredominant symptoms in association with dyspepsia and normal esophagogastroduodenoscopy (EGD) results, and may then be called 'reflux-like dyspepsia'. Ulcer-like dyspepsia is characterized by epigastric pain as the predominant symptom, whereas dysmotility-like dyspepsia is characterized by nausea, vomiting, early satiety, bloating and/or distention. There is marked overlap among these subgroups (4). There may be some rationale for using these symptom subgroups (5); recent trials of the use of proton pump inhibitors (PPI) to treat patients with FD have shown that this symptomatic approach may prove to be useful, but only in the patient who has been investigated and has been found to have NUD. It is time to rethink the approach to the patient with dyspepsia; however, until the patient has an EGD, they have uninvesti-

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gated dyspepsia (UD) and not NUD. Only a minority of patients with dyspepsia require investigation; therefore, the family physician or general practitioner usually deals with UD.

The definition of dyspepsia is further confused because heartburn-predominant symptoms are usually considered to be part of the spectrum of GERD, yet reflux-like dyspepsia is also considered to be part of the spectrum of GERD. GERD has been redefined recently to include the following (6):

> *…all individuals who are exposed to the risk of physical complications from gastroesophageal reflux, or who experience clinically significant impairment of health-related well-being due to reflux symptoms, after adequate reassurance of the benign nature of their symptoms.*

The term 'endoscopy-negative reflux disease' has been defined in the Geneva Workshop Report (6) as,

> *…applying when individuals who satisfy the definition of gastroesophageal reflux disease have neither Barrett's esophagus nor definite endoscopic esophageal mucosal breaks.*

There are limitations to the use of esophageal pH monitoring as the only way to diagnose GERD because patients without reflux esophagitis are misclassified for the presence or absence of reflux disease when only the value of the acid exposure time is used (7). In addition, endoscopy-positive reflux disease must be reconsidered because erythema, friability, edema and blurring of the squamocolumnar junction are unreliable indicators of esophagitis. Finally, it is the utility of symptoms or signs to predict a favourable outcome that is important to the patient. Thus, it may be difficult to distinguish GERD from FD.

INTRODUCTION TO DYSPEPSIA

The approach to the patient with dyspepsia has been reviewed (8). Dyspepsia is a common reason for consultations with family physicians or gastroenterologists (4,9-13), and is responsible for 2% to 5% of visits to primary care physicians (14); however, only approximately one person in four with dyspepsia seeks medical care (15). When the EGD is normal, as is the case in approximately half of people with dyspepsia (16-18), the condition is referred to as NUD or FD, which contrasts with normal endoscopy reflux disease (NERD) (also known as 'endoscopy-negative reflux disease'), where heartburn and regurgitation are the predominant symptoms and EGD results are normal, and UD, where the cause of the dyspepsia is diagnosed clinically without EGD. Are EGD results usually normal in people with dyspepsia with no alarm symptoms? Yes. In 14 studies reviewed by Rabeneck and coworkers (19), 1.6% to 8.2% of patients with dyspepsia had gastric ulcer (GU), 2.3% to 12.7% had duodenal ulcer (DU), 1% to 17.6% had erosive esophagitis (EE) and 0% to 3.4% had gastric cancer (GC). Thus, 50% to 70% of people with dyspepsia have normal EGD results (20,21). It is important to stress that GC is very uncommon in persons younger than 45 years (22,23).

PATHOGENESIS

The cause of NUD is unknown, but speculations include acid hypersecretion, dysmotility, visceral hypersensitivity, psychological factors or chronic active gastritis due to *Helicobacter pylori* infection (24). Subclassification of the symptom complexes of dyspepsia into reflux-like, dysmotility-like and ulcer-like dyspepsia has been attempted. There is considerable overlap among these subgroups, and the usefulness of this approach has been challenged because the pathogenic mechanisms remain to be established. Nonetheless, ulcer-like dyspepsia has symptoms similar to those of ulcer disease, as the name suggests (25). Some *H pylori*-infected NUD patients later develop peptic ulcer disease (25,26), and their acid secretion may be increased compared with that of controls (27,28). Furthermore, motor abnormalities in the stomach and small intestine occur in a varying proportion (10% to 65%) of persons with dysmotility-like dyspepsia (29-35). Also, the relation between gastric emptying abnormalities and symptoms may be poor (32,34,36-38). The symptoms of dyspepsia may overlap with those of irritable bowel syndrome (25,39,40), although the association is not always good (33,35,40-43).

A recent study (44) shed some light on possible etiopathogenetic mechanisms. In a study of 304 persons with chronic FD, 57% could not be easily classified as having 'prevalent pain' or 'prevalent discomfort' (postprandial fullness and/or nausea and/or vomiting). Patients with prevalent pain were more likely to be *H pylori*-infected (81% compared with 60%) and were less likely to have delayed gastric emptying (6% compared with 40%). The pathophysiological abnormality (abnormalities) in patients with reflex-like, ulcer-like or dysmotility-like FD is (are) unknown. Theories include increased acid secretion in response to the infusion of gastrin-releasing peptide (GRP) (28) (but normal basal and peak acid output [45]), chronic active gastrulas due to *H pylori* infection (46), decreased pancreatic bicarbonate secretion (47), stress (16), augmented nociception (48) and gastric motor dysfunction (33), including decreased compliance in the proximal stomach (36,49).

MANAGEMENT STRATEGIES: THE ROLE OF EMPIRICAL THERAPY, PROMPT ENDOSCOPY, AND TESTING FOR *H PYLORI*

There is controversy regarding the best approach to the care of patients with dyspepsia (23). Because of the relatively limited access to upper endoscopy (using EGD), as well as the cost and patient inconvenience, alternative management approaches to prompt endoscopy have been developed. Because at least half of all dyspeptic patients without alarm symptoms have a normal EGD, attempts have been made to try to reduce the use of what some would believe to be an unnecessary procedure. However, EGD may provide the patient with reassurance (50), and cost-benefit studies suggest that EGD before treatment may actually decrease the overall cost of the care of the dyspeptic patient (51). EGD may not be needed in dyspeptic patients younger than 55 years, or in the absence of alarm symptoms such as weight loss, anemia,

dysphagia, vomiting, jaundice, failure of several treatments or strong family history of cancer (22,52,53). The available Canadian data suggest that serious lesions are not missed with this approach (23).

After the 1985 American College of Physicians' recommendation (50), empirical antisecretory therapy (usually with antacids or H_2-receptor antagonists) became the standard of practice in primary care settings for patients with uncomplicated dyspepsia. A randomized, clinical trial reported that prompt endoscopy was more cost effective than empirical H_2-blocker therapy (51). In Canada, prompt endoscopy is not generally available, so an empirical trial is recommended for primary care physicians to treat uncomplicated symptoms (54).

This is the *H pylori* era. *H pylori* is associated with duodenal and GU disease, and arguably with NUD; however, *H pylori* is also common in asymptomatic persons (55). Because of the link between *H pylori* and peptic ulcer disease, and the higher yield of abnormalities on EGD of *H pylori*-positive compared with *H pylori*-negative dyspeptic patients, algorithms have been developed to attempt to identify dyspeptic persons who can be tested and treated for their *H pylori*, and their symptoms expected to resolve, and who should be investigated further with EGD to identify organic disease (56,57). Thus, a 'test and treat' strategy is suggested as one approach to the investigation of the young dyspeptic patient without alarm symptoms. Fendrick and colleagues (58) found that, to diagnose *H pylori*, noninvasive strategies (serological testing for *H pylori* and treating those who were infected with an empirical antisecretory agent with or without antimicrobial therapy) were associated with lower costs per ulcer cured and costs per patient at one year than was prompt endoscopy with or without biopsies. Silverstein and coworkers (59) found no difference in costs between serological testing for *H pylori* and empirical therapy compared with prompt endoscopy. Briggs et al (60) showed that, after eight years, empirical antisecretory therapy was cheaper than serological *H pylori* testing and that, in patients with dyspepsia known to be infected with *H pylori*, prompt endoscopy was more costly than empirical antisecretory and antimicrobial therapy. The cost of EGD in Canada is only a fraction of the cost in the United States, so this conclusion may not be relevant in Canada; Canadian data are awaited. None of these models used urea breath testing, which would have been associated with fewer false-positive results in a country with low *H pylori* prevalence such as Canada (and thereby avoided unnecessary and inappropriate use of antibiotics or EGD for a false-positive test result). Also, symptom relief and quality of life issues were not considered, and clearly these factors need to be examined within the Canadian context. Finally, it must not be forgotten that prompt endoscopy has some benefits, including patient satisfaction, patient and physician reassurance in establishing a diagnosis, and the provision of a rationale for therapy such as maintenance therapy for EE.

Moayyedi and co-workers (61) undertook a community-based randomized, controlled trial of screening and treating *H pylori* in the population. Subjects between the ages of 40 and 49 years were randomly invited to attend their local primary care centre, irrespective of whether they had any dyspepsia symptoms. Of the 8407 subjects eligible for evaluation, 2329 (28%) were *H pylori* positive. Infected subjects were randomly assigned to omeprazole 20 mg bid, clarithromycin 250 mg bid and tinidazole 500 mg bid for seven days or identical appearing placebo. The primary care notes of the participants were then reviewed two years after random assignment to assess health services related to dyspepsia costs. Of the *H pylori*-positive subjects, 498 (21%) had visited a primary care physician in the previous two years, 251 had been randomly assigned to eradication therapy and 247 had been randomly assigned to placebo. There was a significantly greater decline in the proportion of patients seeking health care for dyspepsia during the two years after random assignment in the group who underwent eradication therapy than in the group who received a placebo (43% compared with 53%, relative risk 0.82; 95% CI 0.68 to 0.99, χ^2 P=0.035). Ten *H pylori*-infected patients with dyspepsia, therefore, need to be treated to prevent one patient's dyspepsia symptoms from returning.

TREATMENT

Investigated dyspepsia: There is controversy regarding the efficacy of H_2-receptor antagonists for the treatment of FD/NUD (5,62): in positive studies, the benefit has been small (5,63,64). The negative studies have also had a small number of participants, and a difference compared with placebo may have been missed (45,60,65). Even meta-analyses of the benefit of H_2-receptor antagonists in FD have been challenged (66).

Potent acid inhibition with PPIs have been used successfully (ie, significantly different from placebo) in patients with FD (7,67). The Scandinavian dyspepsia PILOT Project study found that, for the treatment of 197 FD patients, omeprazole 20 mg bid was superior to placebo (P<0.02) in the complete resolution of symptoms at two weeks (7). In the FROSCH study of 801 FD patients, omeprazole 20 mg was superior to placebo at two weeks (67). Two large studies (the Bond and Opera studies) compared omeprazole 20 mg or 10 mg daily with placebo in 1262 FD patients presenting with pain or discomfort (68). The investigators chose among three major symptom groups: ulcer-like dyspepsia with predominant epigastric pain; dysmotility-like dyspepsia with predominant discomfort (postprandial fullness, early satiety, bloating or belching); or reflux-like dyspepsia with predominant reflux symptoms (heartburn or acid regurgitation). In an intention-to-treat analysis of 1248 people, complete symptom relief was observed in 38% of those taking omeprazole 20 mg compared with 36% in those taking omeprazole 10 mg and 28% in those taking placebo (P=0.0002 and 0.02, respectively). Among those with ulcer-like and reflux-like dyspepsia, complete symptom relief was achieved in 40% and 54% of those taking omeprazole 20 mg, and 35% and 45% of those taking omeprazole 10 mg, respectively, compared with 27% and 23% of those taking placebo (all

P<0.05, except omeprazole 10 mg in ulcer-like dyspepsia, P=0.08). There was no significant benefit of omeprazole over placebo in the treatment of dysmotility-like dyspepsia. Symptom relief was similar in *H pylori*-positive and -negative cases. Interestingly, the difference in the treatment responses was greater in patients recruited by a general practitioner than in patients recruited by a specialist. The reason for this is unclear, but these data may be highly relevant to the type of patient with dyspepsia seen in the community.

It is clear that quality of life outcome measures are important in the assessment of the efficacy of therapy in treatment trials in FD. There is no single questionnaire that can be unequivocally recommended for use in dyspepsia trials. The Gastrointestinal Symptom Rating Scale (GSRS) and the Glasgow Dyspepsia Severity Score have been validated (69,70). The Psychological General Well Being Index measures subjective well-being or distress (69). There was no statistically significant difference in the total score or in the subscale scores among the three treatment arms. The GSRS is a valid and responsive measure of gastrointestinal symptoms (69), and GSRS scores improved in patients who took omeprazole 20 mg compared with those who took placebo (68). Thus, it is clear that omeprazole is superior to placebo in the relief of symptoms in persons with FD, especially in the majority of persons with either ulcer-like or reflux-like dyspepsia.

It is unclear what to do for people who do not respond to a PPI. Some patients, particularly those with dysmotility-like dyspepsia, may improve with prokinetic agents. Prokinetic agents were more effective than placebo in 16 of 21 studies, including two of two studies with metaclopramide, seven of seven with domperidone, and seven of 12 with cisapride (66,71). Finney and colleagues (72) recently updated a previous meta-analysis (66) of the use of H_2-receptor antagonists and prokinetic compounds in patients with FD. By combining the results with those of cimetidine and ranitidine and comparing them with results of domperidone and cisapride, the gastrokinetic compounds had a greater difference in success rates than did the H_2-receptor antagonists. However, this meta-analysis did not include the results of four recent large negative studies that did not support the superiority of prokinetic agents compared with placebo in the treatment of FD. Thus, in the patient with ulcer-like or reflux-like dyspepsia, a trial of a PPI is recommended.

UD: The patient with dyspepsia who presents to her or his family physician with UD must be clearly distinguished from the patient with dyspepsia who has consulted a gastroenterologist and is found to have normal endoscopy results (ie, they have NUD or FD). In the former situation, it is not known whether the patient has DU, GU, EE, GC or FD, whereas in the latter situation these pathological conditions have been excluded. Therefore, the results of studies suggesting that omeprazole may be useful to treat the symptoms of persons with FD do not necessarily apply to people with UD. The real challenge to reduce health care utilization is to determine the appropriate management strategy for the person who presents to the primary care physician with dyspepsia – an empirical trail of potent antisecretory therapy, a test for *H pylori* or a prompt endoscopy.

Gastrointestinal assessment is part of a thorough general history and physical examination, as is an assessment of psychosocial factors. Nondrug approaches are often initiated, including lifestyle changes, education and reassurance. Clearly, if the most bothersome or predominant symptoms are heartburn and regurgitation, GERD may be diagnosed clinically, and the patient is appropriately placed on PPI, H_2-receptor antagonist or prokinetic agent. In such persons with UD, the 'omeprazole test' (omeprazole 40 mg at 09:00 and 20 mg at 21:00 for seven days) was 78% sensitive and 86% specific for diagnosing GERD (73), and may reduce the need for endoscopies. Its role as a diagnostic test for GERD in UD patients needs to be confirmed.

When epigastric pain or discomfort is the most bothersome symptom, what is the evidence for the efficacy of therapeutic classes in UD? In a Danish general practice study of more than 1000 patients with a history of peptic ulcer or reflux disease, Meineche-Schmidt and Krag (74) showed that 50% of those taking omeprazole, 35% of those taking cimetidine (P=0.002) and 36% of those taking placebo (P=0.09) had total symptom relief within two weeks. Four additional studies in patients with UD in a family practice setting showed that superior symptom relief was obtained with omeprazole compared with ranitidine (75,76) or compared with an antacid-alginate combination when used for 16 weeks (60% compared with 44%, respectively) (77,78).

Thus, in the patient with UD, a trial of a PPI is warranted. This approach to the care of patients with UD is used only in the patient under the age of 55 years, in the absence of any alarm symptoms and for a short period of time (usually less than four weeks). If the pain recurs or fails to disappear, prompt endoscopy should be undertaken.

Role of *H pylori* infection: While several pathophysiological mechanisms have been postulated to form a biologically plausible link between *H pylori* infection and dyspepsia, and indeed epidemiological studies have suggested such an association (46), no clearly identified factors support a link between *H pylori* and dyspepsia (79). The role of *H pylori* infection in FD is controversial, but recent evidence suggests that eradication of *H pylori* does not lead to a sustained improvement in the symptoms of FD. For example, in the FROSCH study conducted in Germany, 181 *H pylori*-positive patients with dyspepsia were entered into a double-blind, randomized, controlled study (67). Treatment was with two weeks of either omeprazole 20 mg, or omeprazole 40 mg bid plus amoxicillin 1 g bid. Over the six-month follow-up, similar results were found independent of the treatment or the final *H pylori* status, in terms of both symptoms and quality of life scores. Two large, double-blind, placebo controlled, multinational clinical trials have been completed and failed to show a benefit in eradicating *H pylori* when *H pylori*-positive patients with FD were treated and followed-up for 12 months. In the Optimal Regimen Cures *Helicobacter* Induced Dyspepsia (ORCHID) study (69,80), 370 patients were randomly assigned to one-week treatment

with either omeprazole plus amoxicillin plus clarithromycin (OAC) therapy or placebo. In the Omeprazole plus Clarithromycin and Amoxicillin Effect One Year after Treatment (OCAY) Study (81,82), 328 patients were randomly assigned to one-week treatment with either OAC therapy or omeprazole alone. The main outcome measure in both studies was relief from dyspeptic symptoms. There was no difference among OAC, omeprazole and the placebo arms in terms of relief of dyspepsia or quality of life scores. Dyspepsia subgroups were of no value in predicting treatment success. Interestingly, a later exploratory secondary analysis showed that successful relief of symptoms was more likely if the patient's gastritis healed (32% compared with 17%, respectively; $P<0.05$).

In contrast to these negative studies of the role of *H pylori* eradication in FD, two recent trials have suggested that there may be a benefit from eradicating *H pylori* in FD, especially in CagA-positive cases (83,84). Also, in a study by Gilvarry et al (85), the overall dyspepsia symptom score decreased significantly one year after *H pylori* eradication. The Scottish and Irish studies were from single centres and may not be generalizable, and a surprisingly high percentage of patients had a DU at follow-up (14% compared with 2% in the ORCHID/OCAY trials). The outcomes may have been different if the prevalence of DU in dyspeptic patients in the population in question had been lower.

The European *Helicobacter pylori* Study Group suggested screening dyspeptic patients who were 45 years and younger for *H pylori*, reassuring those who were uninfected and treating *H pylori*-positive patients (86). The recent update of the Canadian *Helicobacter* Study Group (87) recommended testing for *H pylori* with a urea breath test in patients in a family practice setting who presented with ulcer-like symptoms, and offering eradication therapy to patients with dyspepsia who tested positive for *H pylori*. A meta-analysis reported by Delaney et al (88) on the four trials (89-92) comparing an *H pylori* test and treat strategy with early endoscopy suggests that only 30% (95% CI 24% to 36%) of the *H pylori* test and treat patients have further investigation. This test and treat (*H pylori*) strategy appears to be cost effective for young and otherwise healthy patients with dyspepsia, but long term follow-up of this approach needs to be performed in Canada.

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