Consensus guidelines: Agreement and debate surrounding the optimal management of *Helicobacter pylori* infection

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D McNamara, C O'Morain. Consensus guidelines: Agreement and debate surrounding the optimal management of *Helicobacter pylori* infection. Can J Gastroenterol 2000;14(6):511-517.
Helicobacter pylori is a recognized cause of a variety of gastroduodenal pathology. The high prevalence of both *H pylori* infection and related diseases within the community warrants its consideration as a public health care issue. The availability of reliable and safe noninvasive diagnostic techniques coupled with the development of effective and tolerable treatments has enabled primary health care personnel to manage this infection actively. The role of the primary care physician in the future management of *H pylori* infection is thus of central importance. The wealth of evidence produced by over 15 years of research into *H pylori* has expanded the list of disease associations and treatment benefits as well as elucidated the pathophysiological mechanisms involved. As a result, there has been a growing need to harmonize this information with clinical practice and to provide direction for the appropriate management by both specialists and general practitioners.
Several national guidelines have been produced. The areas relating to *H pylori* infection that they considered and their recommendations vary. In 1994, the National Institutes of Health produced globally accepted recommendations for the management of *H pylori*-related peptic ulceration. The broader role of *H pylori* as a gastroduodenal pathogen and a public health care issue was not addressed. Recently, European and Canadian consensus guidelines have been published that identified overall management issues, including the role of primary and specialist care, and considered the appropriateness of employing eradication therapy for the spectrum of conditions in which *H pylori* has a direct or indirect association based on the available information. These guidelines, while in agreement regarding many issues, differ considerably in their recommendations for primary health care and regarding central issues such as the management of dyspepsia and gastric cancer. Some variations may reflect differing health care structures as well as the prevalence of both infection and associated diseases. However, the interpretation of evidence produced by recent research contributes to their conflicting statements.

Key Words: *Gastroesophageal reflux disease;* Helicobacter pylori; *Mucosal-associated lymphoid tissue lymphoma; Nonulcer dyspepsia; Peptic ulcer disease*

Directives consensuelles : Entente et mésentente sur le traitement optimum de l'infection à *Helicobacter pylori*

RÉSUMÉ : On reconnaît le rôle étiologique d'*Helicobacter pylori* dans une variété de pathologies gastro-duodénales. La forte prévalence de l'infection à *H. pylori* et des maladies qui y sont associées au sein de nos populations justifie qu'on les considère comme un problème important de santé publique. L'accessibilité à des techniques diagnostiques fiables, sûres et

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Received for publication July 24, 1998. Accepted June 30, 1999

non effractives, alliée à la mise au point de traitements efficaces et tolérables, a permis aux médecins de premiers recours de traiter énergiquement cette infection. Le rôle du médecin de premiers recours dans le traitement futur de l'infection à *H. pylori* est donc d'une grande importance. Toutes les preuves accumulées en plus de 15 ans de recherche sur *H. pylori* a contribué à permis d'identifier de nouveaux liens de cause à effet, de nouveaux rôles thérapeutiques et a fait avancer nos connaissances sur les mécanismes pathologiques en jeu. Il est donc nécessaire à présent d'harmoniser ces données avec la pratique clinique et d'offrir des orientations thérapeutiques appropriées, pour le spécialiste comme pour l'omnipraticien.

Plusieurs directives nationales ont été rédigées, mais n'accordent pas toutes la même importance aux différents aspects de l'infection à *H. pylori* et leurs recommandations varient. En 1994, les *National Institutes of Health* ont produit des recommandations globalement acceptées pour le traitement de l'ulcère gastro-duodénal lié à *H. pylori*. Le rôle plus large de *H. pylori* en tant qu'organisme pathogène gastro-duodénal et le problème de santé publique qu'il représente n'ont pas été mentionnés. Récemment, des directives consensuelles européennes et canadiennes ont été publiées. Elles identifient les enjeux thérapeutiques globaux, y compris le rôle des omnipraticiens et des spécialistes, et se sont penchées sur le bien-fondé d'un traitement d'éradication touchant l'éventail des maladies auxquelles *H. pylori* est directement ou indirectement associé sur la base des renseignements disponibles. Ces directives, bien qu'elles concordent sur de nombreux points, divergent considérablement sur le plan des recommandations destinées aux omnipraticiens et du défi majeur que représente le traitement de la dyspepsie et du cancer de l'estomac. Ces disparités peuvent être le reflet de systèmes de soins de santé différents et de la prévalence spécifique de l'infection et des maladies qui y sont associées. Par contre, l'interprétation des résultats de récents travaux de recherche contribue à la cristallisation de ces divergences.

Helicobacter pylori is one of the most common gastrointestinal pathogens worldwide. Prevalence rates vary geographically, being more common in developing countries and increasing with age and lower socioeconomic status (1). Its association with gastroduodenal pathology, in particular peptic ulceration, peptic ulcer disease (PUD) and gastric mucosal-associated lymphoid tissue (MALT) lymphoma, has revolutionized the management of these conditions. The explosion of research and rapid expansion of our knowledge of related conditions, pathophysiology and treatment options have led to some confusion and considerable debate with regard to the appropriate and optimal management of *H pylori* infection. In order to address these issues and to harmonize patient care, national guidelines were produced. Before the publication of the European consensus guidelines, up to 10 national guidelines had been published that varied greatly in their repertoire, structure, contributors and eventual recommendations. The majority of patients with dyspepsia are initially reviewed in community-based facilities. A proportion of sufferers are infected with *H pylori*, and a subset have related gastroduodenal pathology. As such, community-based testing and appropriate treatment have the foreseeable benefits of improving the patients condition while reducing the need for referral and subsequent use of endoscopy with resultant financial savings. The advent of safe and effective noninvasive testing, and refinement of treatment regimens have brought previous theoretical management strategies into practice.

The Maastricht consensus meeting of September 1996 was proposed to update current guidelines based on available additional information and to consolidate management approaches within Europe. Contributors included representatives of national societies of gastroenterology, invited experts from America, Japan and Canada, representatives of the biomedical industry with an interest in *H pylori* and neutral observers. General practitioners were also represented to highlight the need for community guidelines and to contribute actively in their establishment. The Maastricht consensus promotes both the diagnosis and treatment of *H pylori* within the community and gives clear recommendations for specialist care (2). The Canadian Association for Gastroenterology also held a consensus conference and produced a position statement regarding the role of *H pylori* in dyspepsia, with reference to management options (3). The conclusions of these statements vary over the issues of primary care and the additional disease associations other than PUD and gastric MALT lymphoma, for which eradication therapy is employed. This lack of concordance may reflect regional variations in infection rates and incidence of related conditions. In addition, differences in the interpretation of recent research findings and their relevance within a given health care structure may contribute to these discrepancies.

For over a decade, it has been known that successful eradication of *H pylori* infection in cases of PUD result in not only ulcer healing but also prevention of the development of complications (4,5). Yet it was only in 1994 that the National Institutes of Health recommended routine testing for *H pylori* in cases of PUD and subsequent treatment (6). The acceptance of this strategy is thus recent despite overwhelming supportive evidence. More recent developments will likewise meet with resistance due to the less conclusive association and caution of many practitioners. Therefore, a worldwide consensus is needed to dispel confusion and to promote acceptance of *H pylori* as a public health care issue, lest it becomes obscured among the avalanche of conflicting statements.

CONSENSUS GUIDELINES

The European and Canadian consensus conferences considered the global implications of *H pylori* infection in the community and derived guidelines for both its investigation and its treatment. In particular, they considered aspects relating to primary care and specialist referral units individually, broadened the diseases for which eradication may be employed and advocated the use of effective treatment regimens based on rigorous intention to treat trials.

DIAGNOSIS

Noninvasive methods of diagnosing *H pylori* infection are becoming more available. The ^{13}carbon urea breath test (UBT) has been accepted as the gold standard, noninvasive test, detecting actual infection, which is useful both before

and after treatment (7). Laboratory-based serological diagnosis has an efficacy similar to that of UBT when validated locally but is hampered in its use after treatment because it requires several months for antibody levels to fall sufficiently (8). Both guidelines support the use of noninvasive tests in selected patients – younger than 45 years and younger than 50 years, respectively, and without alarm symptoms. In addition, there is agreement that post-treatment confirmation of eradication is not necessary for uncomplicated cases in the absence of symptoms. Invasive, endoscopic techniques should be employed in all older subjects or in those with alarm symptoms suggestive of complicated PUD, malignancy or other disease entities. The use of noninvasive testing has been recommended not only in specialist centres but also by community practitioners. The debate centres around who should be tested. There is universal agreement that asymptomatic patients should only undergo testing for the purpose of research if there is a strong family history of gastric cancer or if an individual requests testing. In addition, a decision to perform a diagnostic test should only be undertaken if the intention is to treat the infection subsequently. There is a discrepancy with regard to patients presenting with dyspepsia. The Canadian consensus is that patients may undergo testing as assessed on a case by case basis; it is recommended that patients with symptoms consistent with chronic peptic ulcer or those known to have a history of PUD be tested, while individuals with predominant reflux or dysmotility-like symptoms should be excluded. The European guidelines promote the routine testing of all young patients with dyspepsia regardless of the symptom complex. Differences in these recommendations are based on the interpretations of research exploring the role of *H pylori* in dyspepsia and the possible advantages of treating patients with nonulcer dyspepsia (NUD). In addition, there is disagreement over the appropriateness of diagnosing *H pylori* infection in patients with gastroesophageal reflux disease (GERD) requiring long term acid suppression, patients who require and who are taking nonsteroidal anti-inflammatory drugs (NSAIDs) and those with early gastric cancer or premalignant conditions. Briefly, Canadian recommendations do not advise testing in these circumstances because there is insufficient evidence to prove any benefit from subsequent treatment, while European guidelines support diagnosis of *H pylori* infection and treatment in such cases, classifying their recommendation as 'advisable' with respect to the long term use of proton pump inhibitors (PPIs) and NSAIDs, and 'strongly advisable' in cases of early gastric cancer and premalignant conditions.

TREATMENT INDICATIONS

In all cases of PUD, the eradication of *H pylori*, if present, is recommended. The use of eradication therapy has been expanded by both groups to include MALT lymphoma with specialist follow-up, severe or progressive gastritis, and dyspepsia, on a case by case basis in Canada. Again, the two statements disagree with regard to the use of eradication therapy in cases of GERD, gastric cancer and patients prescribed long term NSAIDS. The indications for treatment are given in Table 1.

TABLE 1
Indications for treatment

Indications	Canada	Europe
Peptic ulcer	Yes	Yes
Complicated peptic ulcer disease	Yes	Yes
Mucosal-associated lymphoid tissue lymphoma	Yes	Yes
Severe gastritis	Yes	Yes
Gastric cancer "progressive"	No	Yes
Nonulcer dyspepsia	No*	Yes
Gastroesophageal reflux disease and proton pump inhibitors	No	Yes
Nonsteroidal anti-inflammatory drugs	No*	Yes
High risk of gastric cancer	Yes	Yes
Asymptomatic	No	No
Cancer prevention	No	No
Extraintestinal	N/A	No

**Anti-*Helicobacter pylori *treatment may be employed in patients taking nonsteroidal anti-inflammatory drugs who present with a peptic ulcer. Nonulcer dyspepsia may be considered on a case by case basis. N/A Not considered specifically*

There is unanimous agreement that all treatment regimens employed should have success rates in excess of 80% as assessed by rigorous intention to treat trials. Treatment regimens should be safe, convenient and have minimal side effects. Both working groups advocate the use of PPI-based triple therapy regimens, combining amoxycillin with either clarithromycin or a nitroimidazole for one week as the first-line treatment of choice for *H pylori* infection. Patients in whom treatment fails may undergo eradication with second-line agents or may undergo invasive testing and culturing for sensitivity analysis. There is, in general, consensus between the European and Canadian guidelines; however, the differing approaches to particular conditions require further discussion.

DYSPEPSIA – TEST AND TREAT VERSUS A CASE BY CASE MANAGEMENT APPROACH

Dyspepsia – defined as persistent or recurrent pain centred in the upper abdomen – is a common condition (9). It has been estimated to affect 20% to 40% of the population annually and has a prevalence rate nearing 25% in the developed world (10). It accounts for 2% to 3% of all general practice consultations and is the third most common presenting complaint (11). It is a considerable financial burden on health care systems as a result of its frequency, patients' use of over-the-counter medications, and overall reduction in quality of life and resultant workdays lost.

Dyspepsia as a symptom may result from a number of disease entities. Fifteen per cent to 20% of patients with dyspepsia have gastroduodenal ulceration, 5% to 15% gastroesophageal reflux and 30% to 60% NUD, with fewer than 2% being at risk of underlying gastric malignancy (12). The risk of cancer increases with age, and fewer than 0.5% of pa-

TABLE 2
Intervention trials: *Helicobacter pylori* eradication in nonulcer dyspepsia

Authors (reference)	Improvement	Follow-up (months)
Frazzoni et al (48)	No	10
Pretolani et al (49)	Yes	8
Lazzarroni et al (50)	Yes	6
Patchett et al (51)	Yes	12
Trespi et al (52)	Yes	6
Veldhuyzen van Zanten et al (53)	No	6
McCarthy et al (54)	Yes	12
Elta et al (55)	No	34
Sheu et al (8)	Yes	12
Gilvarry et al (56)	Yes	12
Talley et al (30)	No	12
McColl et al (58)	Yes	12
Blum et al (32)	No	12
Talley et al (33)	No	12

tients with dyspepsia under the age of 45 years have gastric cancer (13). It has been clearly demonstrated that symptoms are a poor indicator of the underlying diagnosis, with the majority of patients describing classical 'heartburn' having neither endoscopic nor pH probe evidence of reflux (14). It is thus imprudent to attempt to define an endoscopic diagnosis based on symptom complex.

H pylori is, as previously stated, a common infection in the community, with 15% to 30% of the population of the developed world being infected (15). It is known to account for 90% of duodenal and 70% of gastric ulcers. In addition, studies have confirmed an increased incidence of infection in individuals with dyspepsia (48%) and with specific conditions (NUD 30% to 60% and distal gastric cancer 70% to 90%) (16). Thus, of the conditions commonly diagnosed following endoscopic examination of patients with dyspepsia, apart from GERD, *H pylori* infection occurs more frequently than in the community. The pathophysiological mechanisms by which infection results in disease have been clearly demonstrated for PUD but remain to be fully explained for NUD and gastric cancer. However, there is strong epidemiological evidence to support a casual role for this infection in both conditions, with seropositivity conferring significant relative risk of subsequent disease development.

NUD

A meta-analysis of epidemiological evidence has suggested an overall twofold increased relative risk of developing NUD in subjects who are *H pylori* positive (17). The possible pathophysiological mechanisms involved have been explored and include acid hypersecretion, altered gastric emptying, increased mucosal permeability, increased cytokine and prostaglandin production, altered nociception and smooth muscle cell dysfunction. The diversity of possible abnormalities reflects the lack of definitive evidence to relate clearly any one mechanism with the development of NUD. Several groups have attempted to establish subgroups based on ulcer, reflux and dysmotility-like symptoms, suggesting that differing disease processes may be involved in each group. Studies to date have been inconclusive (18).

The results of intervention studies have added weight to the association of *H pylori* with the subsequent development of NUD. Several groups have employed eradication therapy in cases of NUD; the results have not been unanimous and the study designs variable (19-29) (Table 2).

However, a meta-analysis of all intervention trials concluded that, in at least a subset of patients with NUD and *H pylori* infection, eradication was of benefit in the long term (19). More recently, two large prospective controlled trials were reported (31-33); their findings were at odds with regard to the overall symptom improvement inferred by active treatment. They both showed that, where there is gastric inflammation, its resolution is associated with an improvement in symptoms. *H pylori* is always associated with an active chronic inflammatory process, and as such, it appears logical to eradicate this infection and, as a result, heal the associated gastritis, which may take up to one year, perhaps explaining the long time lag observed between treatment and subsequent symptom improvement. Despite conflicting evidence, eradication of *H pylori* infection in patients with NUD appears to confer an advantage with regard to symptom improvement in the long term, thus, not only supporting a role for this infection in NUD but also offering an appropriate treatment option other than symptomatic therapy. A recent meta-analysis by Jaakimainen et al (34) supports a role for *H pylori* eradication in the management of NUD.

The majority of patients with dyspepsia have NUD; therefore, a test and treat management strategy means that eradication is employed for either PUD or NUD. As these intervention trials have reported, such an approach is of benefit to at least a subset of NUD patients. In addition, there is evidence to show that there are considerable financial savings to be made by employing such a management strategy. The interpretation of these studies can, in general, explain the difference in the recommendations put forward by the European and Canadian groups. There exists the risk of exposing individuals who will not benefit from treatment to the side effects of eradication regimens and also the possible promotion of antibiotic resistance in failed treatment groups. However, the side effects of the recommended eradication regimens are rarely serious and the consumption of antibiotics in the community for other conditions is staggering in comparison to the quantity employed in eradication regimens. These risks are probably outweighed by the potential benefits. Preventive medicine is common in medical practice, for example, the mass use of antihypertensive and lipid-lowering agents to prevent the development of atherosclerosis and related conditions. Similarly, the eradication of *H pylori* in patients with NUD, even if they fail to improve symptomatically, may benefit in the long term by reducing their risk of subsequent serious sequelae, namely gastric carcinoma and PUD.

GASTRIC CANCER

Gastric carcinoma remains a significant cause of morbidity and mortality in the developed world, despite a declining incidence (20). There is considerable regional and race variability in incidence rates. *H pylori* infection has been associated with the development of this malignancy, based mainly on the findings of a number of epidemiological studies (21-27) (Table 3). The increased relative risk has been estimated to be as high as 8.7, with individuals who are *H pylori*-positive having an overall 1% chance of developing gastric cancer in a lifetime (28). The weight of epidemiological evidence is such that, in 1994, the International Association for Research on Cancer classified *H pylori* as a type 1 carcinogen (29). The majority of individuals with this infection do not develop gastric cancer. At risk groups cannot yet be identified based on bacterial, host or environmental factors. The carcinogenic mechanisms involved remain to be fully established. However, there is growing evidence to support the idea of histological progression through chronic active gastritis, atrophy and intestinal metaplasia to dysplasia and eventual adenocarcinoma (35). Possible etiological mechanisms driving this sequence include persistent inflammation and associated alteration in cellular dynamics, perhaps driven by both bacterial virulence factors and an individual's response to infection. There is evidence to support this theory. Several groups have reported an increase in gastric epithelial proliferation in association with *H pylori*-induced inflammation and that this process is reversible in early stages by successful eradication (36-38). A persistent increase in cell proliferation may induce the formation of DNA mutations or alterations, which may result in the formation of malignant cell lines. This remains to be established, but there are preliminary reports to associate DNA damage with *H pylori*-induced mucosal inflammation of mucosa. The regional and race variability in the incidence of gastric cancer may in some way be explained by differing prevalence rates of *H pylori* infection, by different bacterial virulence patterns and by host genetic variability. Environmental factors, which have been previously associated with the development of gastric adenocarcinoma, may also contribute to a region's relative risk. The development of gastric carcinoma appears to be multifactorial with at risk groups, apart from family history and race, yet to be identified. The possibility remains that the eradication of *H pylori* infection may slow or prevent the development of gastric carcinoma in susceptible individuals. The question remains, at what stage will eradication of infection infer any benefit? The results of studies are conflicting. There have been reports of improvement in gastric atrophy and intestinal metaplasia following eradication. Uemara et al (39) reported that successful eradication led to the suppression of gastric cancer development in subjects who had undergone endoscopic resection of early gastric cancers. Other groups have found no benefit from *H pylori* eradication in patients with atrophy or intestinal metaplasia. It is probable that the carcinogenic process becomes autonomous at some stage in tumour progression and that earlier intervention is required to establish any significant benefit. In view of these findings, some groups have considered the use of mass population screening and treatment. To date, such an undertaking cannot be advocated in the developed world because the financial implications are huge and the overall benefits undetermined (40). However, the results of ongoing intervention studies and the identification of an at risk group may enable selective and cost effective screening in the future. Both the European and Canadian guidelines support the testing and treating of at risk groups, namely those with a family history and certain racial groups. In addition, the European group advocates the use of eradication therapy in cases of early gastric cancer in an attempt to slow disease progression. The use of mass population screening is not supported by either group. The employment of a test and treat strategy for dyspepsia will have the possible long term benefit of preventing disease development in a subset of infected individuals.

TABLE 3
Epidemiological studies to associate *Helicobacter pylori* infection with gastric carcinoma

Author (reference)	Country	Odds ratio	Cases (n)	Controls (n)
Blaser et al (21)	Japan	2.1	83	67
Asaka et al (22)	Japan	2.6	88	75
Kikuchi et al (23)	Japan	13.3	89	39
Fukuda et al (24)	Japan	1.7	76	74
Forman et al (25)	United Kingdom	2.8	69	47
Parsonnet et al (26)	United States	3.6	84	61
Nomura et al (27)	United States	6.0	94	76

NSAIDs AND *H PYLORI*

NSAIDs are among the most commonly prescribed therapeutic agents; approximately 1% of Americans use these drugs daily (41). With the advent of over the counter NSAID sales, it is likely that these numbers will increase. While they are effective anti-inflammatory agents, NSAIDs are responsible for considerable mortality and morbidity. The use of NSAIDS infers a threefold increased risk of gastrointestinal bleeding and is associated with an increased ulcer-related mortality in the elderly (42). There has been growing interest in the possible interactions between NSAIDs and *H pylori* infection. *H pylori* is the most common cause of PUD in all age groups. The prevalence of infection increases with age, as does the risk of NSAID-related mucosal injury. The chemical gastritis induced by these drugs, like the gastritis induced by *H pylori*, most frequently involves the gastric antrum. The possibility of a synergistic effect exists. To date, few trials have established any benefit of *H pylori* eradication in subjects who require NSAIDS. Two groups have shown that the successful treatment of *H pylori* infection reduces the risk of NSAID-induced ulceration (43,44). In addition, Porro et al (45) reported that the successful eradication of *H pylori* infection in subjects who present with a peptic ulcer and who are taking NSAIDs results in

a reduction in ulcer recurrence rates. The findings were not, however, statistically significant (45). The eradication of *H pylori* is supported by Canadian guidelines when a person prescribed NSAIDs presents with a peptic ulcer. The Maastricht consensus also supports the prospective screening and subsequent treatment of patients who are to commence and who are on long term NSAID therapy, thereby reducing the concomitant risk inferred by infection and the use of these agents. These recommendations are classed as 'advisable' based on 'equivocal' evidence.

PPIs AND *H PYLORI* INFECTION

PPIs are powerful antacids and are the mainstay of treatment for GERD. GERD is often a chronic condition requiring long term maintenance therapy. In the presence of *H pylori*, the efficacy of these agents is known to increase compared with that of controls. Recent reports have raised the possibility of deleterious effects from the long term use of these agents in conjunction with *H pylori* colonization of the gastric mucosa. Kuipers et al (46) reported that *H pylori*-positive patients prescribed long te6rm PPIs had an increased risk of developing gastric atrophy, a precursor of malignancy, compared with controls. A more recent study confirmed these findings and also reported an increase in cellular proliferation in such cases (47). These studies have also been contradicted. The possibility of promoting the development of premalignant histological entities prompted the Maastricht Consensus Group to advise the prospective screening and treatment of patients on long term PPIs for *H pylori* infection. The Canadian consensus group was more cautious, citing the need for additional information. They stated that, if a patient was already known to be infected and requiring maintenance PPIs, treatment could be considered on a case by case basis.

CONCLUSIONS

The European and Canadian consensus guidelines were established to harmonize patient care and to clarify new management issues relating to *H pylori* infection. Their recommendations are generally in agreement but differ slightly over the issues previously discussed. The European guidelines have quantified their recommendations as 'strongly advisable', 'advisable' or 'inadvisable', based on the strength of available evidence. The Canadian group's approach was to recommend management strategies for which unequivocal supportive evidence was available. In situations where the issues were less clear, the group advised practitioners to assess each situation on a case by case basis. This difference in these two approaches has ultimately affected their prospective recommendations for the management of dyspepsia in the community. The European guidelines support the routine screening of all young patients with dyspepsia without alarm symptoms by noninvasive techniques and the subsequent treatment of positive subjects. This strategy effectively means that eradication therapy will be employed in the majority of cases of PUD and NUD, for which there are 'strong' and 'advisable' recommendations, respectively. In addition, some patients will receive eradication therapy for GERD, although there is no evidence to casually link *H pylori* infection with this condition and treatment is unlikely to improve symptoms; however, the successful eradication of *H pylori* colonization in these patients may infer a long term advantage by reducing the risk of subsequently developing gastric carcinoma.

The Canadian group has advised noninvasive testing and treatment in younger patients with dyspepsia whose symptoms are suggestive of chronic PUD or in whom a diagnosis of PUD has already been made. Symptoms are a poor predictor of endoscopic diagnosis and are unlikely to actively screen patients with reflux or NUD. A general approach to dyspepsia is not recommended because the evidence to support any beneficial role in conditions other than PUD is less than ideal. The case by case assessment of such conditions has been promoted, but by which criteria and by whom – primary care physician or specialist – have not been elucidated. The possibility exists that, without specific and consistent guidelines, different management practices will develop together with individual practitioners determining the possible advantages and disadvantages of treatment in any one case. Such a situation is less than ideal, particularly in a general practice setting where new evidence produced from ongoing research is not as readily at hand.

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