

Etiology of dyspepsia: Implications for empirical therapy

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Dyspepsia describes a symptom complex thought to arise in the upper gastrointestinal tract and includes, in addition to epigastric pain or discomfort, symptoms such as heartburn, acid regurgitation, excessive burping or belching, a feeling of slow digestion, early satiety, nausea and bloating. Based on the evidence that heartburn cannot be reliably distinguished from other dyspeptic symptoms, the Rome definition appears to be too narrow and restrictive. It is particularly ill suited to the management of uninvestigated dyspepsia at the level of primary care. In patients presenting with uninvestigated dyspepsia, a symptom benefit is associated with a 'test and treat' approach for *Helicobacter pylori* infection. A substantial proportion of those who do not benefit prove to have esophagitis on endoscopy. In those with functional dyspepsia, the benefits of *H pylori* eradication, if any, appear to be modest. Hence, a 'symptom and treat' acid-suppression trial with proton pump inhibitors, and a 'test and treat' strategy for *H pylori* are two acceptable empirical therapies for patients with uninvestigated dyspepsia.

Key Words: *Dyspepsia; Empirical therapy; Functional dyspepsia; Uninvestigated dyspepsia*

Étiologie de la dyspepsie : Implications pour le traitement empirique

RÉSUMÉ : La dyspepsie désigne un complexe de symptômes dont l'origine se situerait au niveau du tractus digestif supérieur et qui comprend en plus des douleurs, des malaises gastriques, des symptômes tels brûlures d'estomac, régurgitation acide, irritation excessive, sensation de digestion lente, satiété précoce, nausées et ballonnements. Comme la brûlure d'estomac ne peut se distinguer de façon fiable d'autres symptômes dyspeptiques, la définition de Rome semble trop étroite et restrictive. Elle est particulièrement mal adaptée à la prise en charge empirique de la dyspepsie en médecine de premiers recours. Chez les patients qui se présentent pour une dyspepsie n'ayant pas fait l'objet d'épreuves diagnostiques, on constate un avantage sur le plan des symptômes avec l'approche «tester et traiter» pour l'infection à *Helicobacter pylori*. Une proportion substantielle de ceux qui ne se trouvent pas soulagés se révèlent en effet atteints d'œsophagite à l'endoscopie. Chez les sujets qui souffrent d'une dyspepsie fonctionnelle, les avantages de l'éradication de *H. pylori*, le cas échéant, semblent modestes. Ainsi, un essai de suppression acide avec des inhibiteurs de la pompe à protons et une stratégie «tester et traiter» pour *Helicobacter pylori* semblent deux traitements empiriques acceptables chez les sujets souffrant de dyspepsie n'ayant pas fait l'objet d'investigation.

In Canada, approximately two-thirds of adult patients with upper gastrointestinal symptoms have an identifiable lesion on upper gastrointestinal endoscopy (esophago-gastroduodenoscopy [EGD]), most commonly erosive

esophagitis (1). In patients with dyspepsia and a normal EGD, evidence suggests that a number of abnormalities, including disordered neuromuscular function or nociception, may drive symptom expression. Slow or incomplete

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resolution of such abnormalities may explain persistent symptoms after suspected triggers of injury, such as *Helicobacter pylori* infection, have been eliminated. These concepts have developed concurrently with a substantial change in the prevalence of known causes of upper gastrointestinal symptoms, particularly a declining incidence of peptic ulcers and an increasing incidence of gastroesophageal reflux disease (GERD). Both have implications for the rational selection of empirical therapies and the use of diagnostic procedures.

The Canadian *Helicobacter* Study Group met in Ottawa, June 22 to 24, 2001. The names of the participants are listed in Appendix 1. This document reflects the consensus of the discussions and is approved by the attendees. Equal at-arms¹-length financial support was received with appreciation from Abbott Laboratories Limited, AstraZeneca Canada Inc, Axcan Pharma Inc, Glaxo Wellcome and Solvay Pharma/BYK Inc.

DEFINITIONS AND PREVALENCE OF DYSPEPSIA

Dyspepsia, a disorder in which epigastric pain or discomfort is the major symptom, encompasses a broad range of upper gastrointestinal symptoms of varying intensity, description and location. The underlying cause of these symptoms is usually benign, but serious disease, such as gastric cancer, rarely may be present. The prevalence of dyspepsia in the general adult population is estimated to range between 20% and 45% (2-4). In a population-based study in Canada, 29% of those surveyed reported persistent or recurrent symptoms within the preceding three months, whereas only 34% of this sample population had never experienced significant dyspepsia (5).

Despite evidence that only a small proportion of these patients seeks medical attention (6), dyspepsia is the fourth most common complaint in patients seen in primary care (7). The presentation of dyspepsia may include a variety of symptoms such as retrosternal or epigastric burning, belching, burping, nausea, bloating or a feeling of slow digestion. By definition, dyspepsia involves epigastric symptoms, but it may be difficult to isolate epigastric symptoms from heterogeneous complaints referable to other areas of the body. There has been particular controversy about the diagnostic reliability with which heartburn, defined as a burning retrosternal pain radiating upwards toward the mouth, can be distinguished from epigastric pain. Dyspepsia criteria relevant to primary care practice that exclude heartburn and other symptoms of GERD are too restrictive due to symptom overlap or ambiguous complaints. Moreover, studies of both primary care physicians and specialists demonstrate poor discrimination of GERD and peptic ulcer disease on the basis of clinical symptoms alone (8).

Dyspepsia is not a diagnosis, but rather a symptom or symptom complex suggestive of an upper gastrointestinal tract source. Efforts to treat the dominant symptom, as recommended in the Rome criteria (9), or symptom clusters, as recommended in a subsequent modification of the original

Rome criteria (10), are hampered by the fact that a high proportion of patients have multiple, overlapping symptoms, or symptoms that fit poorly into a single category. In addition to heartburn and regurgitation, which are characterized as reflux-like dyspepsia, other symptom subgroups are ulcer-like, signifying focal epigastric pain that is often relieved by meals, or dysmotility-like dyspepsia, with bloating, fullness and/or early satiety. The Rome classifications are intended to guide treatment rather than to diagnose an etiology.

When symptom clusters are used to describe subgroups of patients with dyspepsia, they are characterized as reflux-like in approximately 20% of cases, ulcer-like in 11% and dysmotility-like in 7%. Approximately 20% of patients cannot be placed into any of these groups because of symptom overlap, and an additional 40% cannot be categorized because their symptoms are so nonspecific (11). When dominant symptoms, rather than symptom clusters, were used to characterize subgroup patients in a Canadian population-based study, the presentation was characterized as dysmotility-like in 55%, reflux-like in 43% and ulcer-like in only approximately 12% (5).

About two-thirds of patients with dyspepsia, when defined to include heartburn, have endoscopic evidence of reflux esophagitis (1). Peptic ulcer disease is observed in less than 10%. In North America, malignancy is exceedingly rare in subjects with dyspepsia, particularly in those under 50 years of age and who have no alarm features such as weight loss, dysphagia, bleeding or anemia. The remaining patients have a normal EGD and are classified as having functional dyspepsia.

Except for complicated ulcer disease and malignancy, both of which are uncommon in an otherwise healthy population, dyspepsia is usually a relatively benign condition. However, dyspepsia does cause a significant impairment in the quality of life of the sufferer. In a Canadian population-based study, work absenteeism among people with dyspepsia was nine times more frequent than in those without dyspepsia (5). Nonprescription drugs were taken by 51% of those with dyspepsia, versus only 6% of those without symptoms. Patients with dyspepsia also had impairment in objective measures of psychosocial function relative to healthy controls.

ETIOLOGY: CURRENT CONCEPTS

Acid secretion is an important contributor to identifiable causes of dyspepsia, such as duodenal ulcer or GERD. Impaired gastrointestinal motility is also implicated in the pathogenesis of dyspepsia, but its role as an independent factor is much less clear. In patients with functional dyspepsia who are poorly responsive to therapies targeted at either of these factors, there is mounting evidence for a complex relationship between stress, gastrointestinal dysfunction, mucosal injury and symptomatology (12). Current studies are focused on the possibility that functional dyspepsia is a consequence of changes in visceral hypersensitivity, as well as neuromuscular dysfunction, potentiated by activation of

the immune system. Although specific stimuli, including infection with *H pylori*, may play a critical role in initiating dyspepsia, the condition may be slowly resolving or even self-perpetuating once it has been triggered.

An emerging concept regarding the pathogenesis of functional dyspepsia is an interrelationship between the immune system, the afferent nervous system and neuromuscular function (13). Although there may be considerable interpatient differences in the specific sequence of events, altered neuromuscular function and visceral hypersensitivity are likely to occur as a result of the activation of cytokines and neuropeptides secondary to associated inflammation, local tissue injury and stress, or a combination of these.

There is increasing evidence to support the importance of the gut-brain-gut axis in both normal gastrointestinal function and disease. For example, experiments first published a decade ago demonstrated an association between gastrointestinal inflammation and an alteration in central nervous system activity and behaviour (14). Subsequent studies correlating stress with an increased susceptibility for mucosal inflammation indicate that communication between the brain and the gut is bidirectional (15). The presence of inflammation also increases the sensitivity of the intestinal tract to subsequent stress (16). The mechanisms by which persistent changes might be expected to affect neuromuscular function or to sensitize perception to normal gastrointestinal events include altered levels of substance P (a peptide associated with decreased muscle contraction) and activation of afferent nerve pathways.

Functional dyspepsia defines a population of individuals with symptoms but without evidence of macroscopic lesions in the gastrointestinal tract. This does not eliminate the possible release of inflammatory cytokines (either as a precipitating event or as a subclinical process causing dyspepsia), but it does suggest that the relationship is complex. One theory is that the activation of immune factors during an initial episode of inflammation triggers a process that persists after the inflammation has resolved. Cytokines such as interleukin-6 and tumour necrosis factor- α inhibit muscle contraction and alter neural activity, and pathways may be activated even after resolution of obvious mucosal inflammation (17). Moreover, these cytokines may potentiate pathogenic processes by stimulating the release of neuropeptides or other endogenous factors, which in turn alter gastrointestinal function.

In general, dyspepsia associated with peptic ulcer disease and erosive esophagitis resolves with healing of the underlying pathology. The same processes leading to tissue injury and impaired gastrointestinal function in these conditions may have parallels in persons with functional dyspepsia. The presence of injurious agents exacerbated by stress may trigger a cascade of events that include immune activation, increased production of prostanoids and increased production of neuropeptides involved in acid secretion. While inflammation progresses to mucosal damage in only a minority of patients, hypersensitivity of the gut in persons

with functional dyspepsia may persist until the triggers of sensory abnormalities resolve.

In animal models of *H pylori* infection, altered levels of neurotransmitters, such as acetylcholine, and an increase in substance P, calcitonin gene-related peptide and vasoactive intestinal peptide-circulating nerves, indicate the potential for this bacterium to alter neural circuitry in the gastrointestinal tract (13). Experimental data suggest that these changes are not related to the bacterium itself, but rather to the level of the chronic inflammatory response induced by the *H pylori* infection. Many of the changes observed with this infection resolve after the successful eradication of *H pylori*. However, some of the functional and structural changes, such as those induced by an increase in macrophage infiltration and recruitment of mononuclear cells, may persist. This provides a basis for the speculation that eradication may not be sufficient to restore function to normal.

The pathogenicity of the specific *H pylori* strain also could be a factor in the risk of sustained damage. For instance, increased gastric epithelial permeability secondary to *H pylori* infection has been linked to the presence of the vacuolating cytotoxin *vacA* gene (18). By opening intercellular tight junctions in the gastric mucosa, the toxin could increase the risk of an immune response leading to dyspeptic symptoms through the exposure of nerve endings to acid. The opening of tight junctions in the esophageal mucosa by processes unrelated to *H pylori* infection is also a prominent focus of studies attempting to explain symptoms of gastroesophageal reflux in the absence of erosive esophagitis (19).

Changes in mucosal permeability and neuromuscular function leading to functional dyspepsia are not yet fully supported by clinically relevant studies. However, these concepts provide an important direction for understanding the roles of both *H pylori* infection and other pro-inflammatory factors that may initiate similar dysfunction. For example, evidence for comparable events in patients with the irritable bowel syndrome, a functional gastrointestinal disorder not related to *H pylori* infection, support the concept of a disturbance of the gut-brain-gut axis in immune function and neuromuscular activity (20,21). These hypotheses, which also incorporate psychogenic stress as a factor in determining symptom expression, provide a physiological basis for identifying potential new targets for medical therapy.

PRACTICAL MANAGEMENT: CURRENT CONCEPTS

In considering the management of patients with dyspepsia, it is important to differentiate between uninvestigated and investigated (functional) dyspepsia. There may be confusion if these two distinct clinical groups are considered together. When a patient presents for the first time to a primary care physician with dyspeptic symptoms, he or she has not been investigated (uninvestigated), and the cause of their dyspepsia is unknown. The most common diagnoses are GERD, functional dyspepsia, ulcer disease and, rarely,

malignancy. Before embarking on empirical therapy for uninvestigated dyspepsia, a history should be taken to rule out other pathologies, particularly those involving the cardiovascular and hepatobiliary systems. Somatoform disorders may also mimic dyspepsia. Iatrogenic causes of dyspepsia, particularly due to acetylsalicylic acid and non-steroidal anti-inflammatory drugs (NSAIDs), should also be excluded. About 30% of patients on chronic NSAID therapy develop dyspepsia (22), although the risk may be reduced but not eliminated with the use of cyclooxygenase-2-selective inhibitors (23). In patients with mild or intermittent symptoms, lifestyle modifications such as a change in the diet, may be appropriate before embarking on drug therapy, although a benefit from such modification has not been proven (24,25).

Due to the traditional association between dyspepsia and peptic ulcers, first-line empirical therapies for persistent epigastric discomfort have been targeted in ulcer disease. When *H pylori* infection was first recognized as the most important etiological factor for peptic ulcer, a 'test and treat' eradication strategy was widely advocated (26). A 'test and treat' strategy is preferable over antisecretory drugs for possible peptic ulcer, because it can lead to a cure of the underlying disease.

H pylori is a pathogen that causes chronic active gastritis. It is reasonable to consider that this gastritis contributes to upper gastrointestinal symptoms (ie, be one of the causes of dyspepsia) and that eradication of the infection can lead to symptom resolution. Indeed, many consensus conferences have advocated the 'test and treat' approach in the initial management of patients with dyspepsia, despite a lack of convincing evidence from randomized, controlled trials. The Canadian Adult Dyspepsia Empirical Treat – *H pylori* Study (CADET-Hp) provides the first level 1 evidence that *H pylori* eradication improves dyspeptic symptoms in patients with uninvestigated dyspepsia seen at the primary care level (27). The number needed to treat to achieve symptom resolution is one patient in seven. Thus, good evidence now supports such a 'test and treat' strategy for patients seen in primary care with uninvestigated dyspepsia.

However, the prevalence of peptic ulcer disease has been diminishing and, in Canada, endoscopic studies suggest that peptic ulcers, once considered the cause of dyspepsia in up to 25% of patients, are now found in fewer than 10% (1). One explanation for the diminishing incidence of peptic ulcer is the decline in the prevalence of *H pylori* infection. Except in aboriginals and some groups of recent immigrants, the prevalence of *H pylori* infection has fallen to less than 30% in most parts of Canada. In addition, it is now recognized that a smaller proportion of peptic ulcers can be attributed to *H pylori* infection than was previously appreciated. For example, in one study conducted in Montreal, *H pylori* was identified in 95% of patients with peptic ulcers in 1993, but in only 62% in 1998 (28).

These data predict that there will be limited benefits from a test and treat strategy in patients with uninvestigated dyspepsia, based on the cure of an underlying peptic

ulcer. However, theoretical benefits from eradication of an infection that leads to chronic gastritis have also supported this test and treat approach. Yet, the objective evidence of benefit from *H pylori* eradication in functional dyspepsia, including two recent meta-analyses (29,30), has been conflicting. In one analysis of data from seven trials, the odds ratio for a response one month after anti-*Helicobacter* therapy was 29% greater in those receiving eradication treatment versus controls, but it needs to be stressed that this difference was not statistically significant (29). In the other meta-analysis of nine trials, the response rate was 36% in those treated with an eradication regimen compared with 28% among controls ($P < 0.002$) (30). It was estimated that 15 subjects would require therapy to eradicate *H pylori* infection for one patient to benefit.

This relatively low proportion of *H pylori*-positive patients with functional dyspepsia who benefit from cure of the infection is likely due to the complexity of symptom expression, rather than to the absence of a significant relationship of the pathogenesis of dyspepsia with this pathogen. Eradication of *H pylori* infection may well be important but is insufficient for immediate or complete symptom relief. Importantly, the relationship between *H pylori* infection and abnormalities of gastric function provide a context in which to identify mechanisms of neuromuscular dysfunction or altered nociception that are independent of the infection. The details of the endogenous responses to changes in gastrointestinal function are essential for the development of new targets of therapy.

Evidence suggests that the benefit from *H pylori* eradication in patients with uninvestigated dyspepsia is limited to a relatively small subgroup (only about 14% of patients with uninvestigated dyspepsia). Taken together with the declining risk of peptic ulcer disease, these data also question the strategy of test and treat as a first-line empirical management approach, if it is assumed that only patients with peptic ulcer disease benefit. Although previous studies have shown that a test and treat approach is cost effective in an uninvestigated population due to fewer referrals for diagnostic endoscopy (26), indiscriminate eradication of *H pylori* infection in an otherwise tolerant host is being increasingly challenged because of a potential, but undefined, risk to benefit ratio of eliminating what some consider to be normal biota (31). Conversely, a recent study has shown that *H pylori* infection is a significant risk factor for gastric cancer, particularly in patients with dyspepsia (32).

The alternatives to a test and treat strategy for the first-line management of dyspepsia include the use of empirical therapies or early use of endoscopy, which is a reliable but expensive diagnostic tool. While endoscopy should be used early in patients older than age 50 years with new onset dyspepsia, or any individual with alarm symptoms (such as unexplained weight loss, unexplained vomiting, upper gastrointestinal bleeding, anemia, abdominal mass or dysphagia), universal screening is impractical and expensive. Furthermore, virtually all the lesions found in a recent study of 1040 dyspeptic Canadians having a prompt endo-

scopy were amenable to treatment with acid suppression therapy, *H pylori* eradication therapy or elimination of NSAIDs (1).

Of the empirical therapies studied in uninvestigated dyspepsia, proton pump inhibitors (PPIs) are the most likely to provide symptom relief. In clinical trials, significant symptom improvement is observed in almost one-half of patients with ulcer-like symptoms and two-thirds of those with reflux-like symptoms (33). Although PPIs are not superior to placebo in the relief of dysmotility-like symptoms, a response to empirically administered PPI therapy is considered diagnostic for GERD (34). Response rates are high in both those with and those without esophageal lesions at endoscopy. In an empirical antisecretory treatment strategy, PPIs are preferred over H₂-receptor antagonists, because it is expected that the superior acid control will increase sensitivity for both the detection and the treatment of an acid-related disorder.

One risk of initiating empirical acid suppression rather than a test and treat strategy for dyspepsia is the potential delay in establishing a diagnosis of peptic ulcer disease. Although the population at risk of ulcer disease is diminishing, this important concern should be weighed against the patient's clinical presentation and the risk of complications. In otherwise healthy individuals under the age of 50 years, refractory or frequently recurring symptoms after discontinuation of acid suppression therapy and a positive family history of peptic ulcer disease should increase the index of suspicion for a duodenal or gastric ulcer, or for GERD, warranting either an empirical test and treat strategy or endoscopy. In most individuals, however, the relatively low risk of peptic ulcer disease, and the even lower risk of complications from a delayed diagnosis, suggest that a more appropriate first step is to determine whether the dyspeptic symptoms are acid related.

Many patients who are anxious about the possibility of a serious disease, particularly malignancy, often derive reassurance from negative findings at endoscopy. Endoscopy is associated with significant improvements in patient satisfaction (35,36). Although endoscopy is not an appropriate screening tool for dyspepsia, it is a valuable procedure in patients with persistent complaints who are unresponsive to empirical therapies.

Some physicians have the clinical impression that there may be a psychogenic component to functional dyspepsia. However, controlled trials of antidepressants and other psychotropic agents have not consistently demonstrated significant benefit (37). The potential for benefit from psychotherapy in selected patients, particularly any intervention aimed at reducing stress, cannot be completely discounted. The evidence for the importance of gut-brain-gut interactions in functional gastrointestinal diseases should be misinterpreted as a foundation for suspecting hypochondriasis. Anxiolytics should not be considered as primary therapy of dyspepsia, whether uninvestigated or functional, unless there is underlying anxiety for which there is a clear indication to try anxiolytics.

Flexibility is an essential component of treatment algorithms developed for the management of patients with uninvestigated dyspepsia. Clinical impressions are unavoidable, but unaided clinical diagnosis is generally unreliable. In an endoscopically controlled study that compared general practitioners with experienced gastroenterologists, the sensitivity for either group in diagnosing peptic ulcer was only 60% (8). Importantly, nearly one-half of the patients with ulcer or esophagitis were misclassified. There was agreement between the general practitioners and the gastroenterologists in only 45% of cases, and the likelihood of a correct diagnosis correlated poorly with the physicians' degree of conviction of the diagnosis.

In the practical management of dyspepsia, both clinicians and patients must be prepared for some degree of uncertainty. It is the level of acceptable uncertainty that will prompt intervention. Based on current risk factors in Canadians with dyspepsia, empirical antisecretory treatment with a PPI is an appropriate first step in younger patients with symptoms consistent with an acid-related disorder, such as heartburn, acid regurgitation or epigastric pain relieved by food or antacid, particularly when there are no alarm features. Prokinetic agents also might be considered for use in a trial of empirical therapy, but the therapeutic options are limited with the withdrawal of cisapride from the Canadian market. Although current data suggest that only a small proportion of patients obtain symptom relief with *H pylori* eradication, a major benefit of this approach is that one in seven patients is cured of their dyspepsia (27). If a noninvasive *H pylori* test is negative, one can be reasonably certain that an *H pylori* infection is not present and the patient can be reassured that serious pathology is unlikely. If dyspepsia persists, an endoscopy can be performed to provide reassurance. Indeed, the ability to rule out serious organic disease may be the most important contribution of endoscopy in the management of the patient with dyspepsia.

There are few similarities between adults and children in the approach to the diagnosis and treatment of dyspepsia. Upper gastrointestinal symptoms are common in children (up to 10% of the school age population), but these symptoms are less commonly associated with gastrointestinal pathology such as peptic ulcers or esophagitis (38). Whereas treating for *H pylori* infection in adults with dyspepsia will benefit the small proportion who have peptic ulcer disease that would respond to a test and treat strategy, there is little current justification for screening children with dyspepsia for *H pylori* infection (39).

CONTROVERSIAL MANAGEMENT ISSUES AND FUTURE DIRECTIONS

The discovery that *H pylori* infection is a major cause of peptic ulcers has been the impetus to question many assumptions about upper gastrointestinal physiology and pathophysiology. Over the course of the past two decades, the pendulum of scientific opinion has swung back and forth in regard to the nature and role of *H pylori* infection,

and its threat to the human host. Although *H pylori* is a documented pathogen, the majority of those infected tolerate life-long infection with no discernible symptoms. While uniform eradication is a widely cited goal of the efforts to develop a vaccine, most management guidelines now caution against the indiscriminate screening for and eradication of *H pylori* infection.

A further debate, generated by the results of an uncontrolled trial, was the purported risk of gastric atrophy and intestinal metaplasia from the use of long term PPI therapy in patients with *H pylori* infection (40). However, a prospective observational trial comparing long term PPI with fundoplication surgery as a control group, did not show that long term PPI therapy in *H pylori*-infected patients resulted in progression of gastric atrophy (41). A placebo controlled trial of *H pylori* eradication in patients on long term PPI of sufficient duration, however, is still lacking. Thus, at present, good evidence is not available to advocate a strategy of tests for and eradicating *H pylori* in patients on chronic PPI. Furthermore, data to show that this approach is harmful are also lacking.

Less well understood is whether *H pylori* increases the risk of NSAID-induced gastropathy. It is logical to predict that two independent factors for damage to the gastric mucosa would have additive effects on tissue integrity, but studies to date have been contradictory (42). Although it may be prudent to test and treat for *H pylori* in patients who have developed peptic ulcers while undergoing NSAID therapy, the benefits with regard to a diminished risk of ulcer complications caused by NSAIDs have not been documented. Alternative approaches in patients who are unable to discontinue NSAIDs include adding a PPI, changing to a more selective cyclooxygenase-2 inhibitor or adding a mucosal protective agent such as misoprostol.

New agents already entering investigation for the control of dyspepsia include kappa opioid agonists, substance P antagonists, and 5-hydroxytryptamine₃ antagonists. Some of these have already reached clinical testing in other func-

tional gastrointestinal disorders, such as the irritable bowel syndrome. What role these drugs will have in the therapy of dyspepsia is not yet known. However, evidence of efficacy in randomized, controlled trials will dramatically alter our understanding of the causes of dyspepsia, and advance therapies specific to the underlying etiology.

CONCLUSIONS

The diversity of symptoms in patients with dyspepsia appears to be matched by the complexity of underlying pathological factors. *H pylori* eradication is of symptomatic benefit in a small proportion of patients with uninvestigated dyspepsia, and acid suppression with a PPI is effective in many patients, particularly those with heartburn or ulcer-predominant dyspepsia. The optimal approach for some nonresponders is reassurance regarding the absence of a serious underlying disorder, including performing an endoscopy to provide that reassurance. Although eradication of *H pylori* infection in uninvestigated dyspepsia improves symptoms, the symptomatic benefit of *H pylori* eradication in patients with functional dyspepsia is small. The effects of this bacterium on gastrointestinal function promise new clues about the interrelationship between the immune responses and the gut-brain-gut axis in functional gastrointestinal disorders. Details about this interrelationship likely will prove to be relevant to symptom expression for pathogenic triggers in addition to *H pylori* infection. Hence, a 'symptom and treat' acid-suppression trial with PPIs, and a 'test and treat' strategy for *H pylori* infection are two acceptable empirical approaches for patients with uninvestigated dyspepsia.

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APPENDIX 1

Participants in the Canadian *Helicobacter* Study Group meeting, Ottawa, Ontario, June 22 to 24, 2001

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