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An evidence-based approach to the management of uninvestigated dyspepsia in the era of *Helicobacter pylori*

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Special Supplement

Abstract

Objectives: To provide Canadian primary care physicians with an evidence-based clinical management tool, including diagnostic and treatment recommendations, for patients who present with uninvestigated dyspepsia.

Recommendations: The management tool has 5 key decision steps addressing the following: (1) evidence that symptoms originate in the upper gastrointestinal tract, (2) presence of alarm features, (3) use of nonsteroidal anti-inflammatory drugs (NSAIDs), (4) dominant reflux symptoms and (5) evidence of *Helicobacter pylori* infection. All patients over 50 years of age who present with new-onset dyspepsia and patients who present with alarm features should receive prompt investigation, preferably by endoscopy. The management options for patients with uninvestigated dyspepsia who use NSAIDs regularly are: (1) to stop NSAID therapy and assess symptomatic response, (2) to treat with NSAID prophylaxis if NSAID therapy cannot be stopped or (3) to refer for investigation. Gastroesophageal reflux disease can be diagnosed clinically if the patient's dominant symptoms are heartburn or acid regurgitation, or both; these patients should be treated with acid suppressive therapy. The remaining patients should be tested for *H. pylori* infection, and those with a positive result should be treated with *H. pylori*-eradication therapy. Those with a negative result should have their symptoms treated with optimal antisecretory therapy or a prokinetic agent.

Validation and evidence: Evidence for resolution of the dyspepsia symptoms was the main outcome measure. Supporting evidence for the 5 steps in the management tool and the recommendations for treatment were graded according to the strength of the evidence and were endorsed by consensus of committee members. If no randomized controlled clinical trials were available, the recommendations were based on the best available evidence.

Literature review: Evidence was obtained from MEDLINE searches for pertinent articles published from 1966 to October 1999. The searches focused on dyspepsia, diagnosis and treatment. Additional articles were retrieved through a manual search of bibliographies and abstracts from international gastroenterology conferences.

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Dyspepsia is a common condition in Canada (prevalence 29%[1]) that significantly diminishes the quality of life of those affected. Primary care physicians treat most patients with dyspepsia. An estimated 7% of the average Canadian family physician's practice is devoted to the management of dyspepsia, and 23% of these patients are presenting for the first time.[2]

The term "dyspepsia" describes a heterogeneous group of symptoms with nu-

Abbreviations used in this article

AC	amoxicillin + clarithromycin
BMT	bismuth (subsalicylate) + metronidazole + tetracycline
COX-2	cyclo-oxygenase 2
GERD	gastroesophageal reflux disease
H_2-RA	H_2-receptor antagonist
MC	metronidazole + clarithromycin
NSAID	nonsteroidal anti-inflammatory drug
PPI	proton-pump inhibitor
RBC	ranitidine bismuth citrate
UBT	urea breath test

merous underlying causes. One of the challenges for the primary care physician is to determine optimal treatment for the patient presenting with new-onset or previously uninvestigated dyspeptic symptoms. The clinician must decide whether investigations are needed and must determine optimal drug therapy when treatment is warranted. Selection of the appropriate agent, determination of the duration of treatment and an appropriate follow-up plan are then required.

Recognition of the role of *Helicobacter pylori* in the pathogenesis of peptic ulcer disease has revolutionized ulcer therapy and has prompted re-evaluation of the clinical approach to dyspepsia. New data have been published concerning treatment of dyspepsia in patients who harbour and those who do not harbour *H. pylori*. These data have implications for the diagnosis and treatment of uninvestigated dyspepsia in primary care.

Evidence-based medicine combines the best available evidence from the medical literature and clinical expertise to aid decision-making in patient care. The Canadian Dyspepsia (CanDys) Working Group was convened with the mandate to develop an evidence-based management tool for uninvestigated dyspepsia that would be practical and would reflect the realities of the primary care setting. The aim was to provide primary care physicians with recommendations and guidance concerning appropriate investigations, treatments and indications for referral for patients with uninvestigated dyspepsia. The resulting clinical management tool is intended not to regulate practice but, rather, to support clinical decision-making.

Methods

Canadian Dyspepsia Working Group

The 18 members of the working group were selected by the chair (S.v.Z.) because of their expertise in dyspepsia, evidence-based medicine and continuing medical education. Broad representation from across the country was sought. The group is a mixture of university-based and private practice family physicians, gastroenterologists and pharmacists.

All members initially met in Montreal in May 1998 to discuss the aims of the working group, the important elements for inclusion in the management tool and the methods by which the evidence in support of a newly developed management tool would be reviewed. This meeting included several presentations from gastroenterologists and family physicians on important aspects of dyspepsia. It also included case presentations by family physicians, selected from their clinical practices, to ensure that the realities of managing dyspepsia in primary care were addressed adequately. The management tool and associated treatment recommendations, in their final form, are the outcome of several revisions made during 2 additional meetings and through teleconferences.

Review and grading of evidence

Literature review methods for the initial meeting included MEDLINE searches for articles published from 1966 to April 1999 on the following major topics: the definition of dyspepsia, the differential diagnosis and the value of subclassification based on symptoms alone; the prevalence and natural history of dyspepsia; the prevalence of organic disease in patients with uninvestigated dyspepsia; the yield of specific investigations; and evidence in support of various treatments for dyspepsia. Searches relevant to treatment options were conducted for lifestyle modification and for various drug therapies, including antacids, H_2-receptor antagonists (H_2-RAs), prokinetic agents and proton-pump inhibitors (PPIs). The titles and abstracts from the literature search were reviewed, and all relevant articles were retrieved for further evaluation.

Individual working group members compiled the existing evidence on particular topics and provided overviews and summary conclusions of the topics for the entire committee. High-quality reviews, systematic overviews and meta-analyses were considered as a source of evidence. The original studies on which the conclusions of these reviews were based were retrieved and evaluated by the working group to ensure that committee members agreed with the conclusions.

To ensure incorporation of current information by the end of the document revision process, specific searches for clinical trial data up to January 2000 were conducted for PPIs (lansoprazole, omeprazole and pantoprazole) and H_2-RAs (ranitidine, famotidine, cimetidine and nizatidine) as well as the prokinetic cisapride, the cyclo-oxygenase 2 (COX-2)-specific inhibitors celecoxib and rofecoxib, and ranitidine bismuth citrate. Searches included only articles written in English and were limited to data for human subjects. A summary of these searches related to treatment recommendations is given in Table 1 for each mini-management schema. The most relevant articles were retrieved and reviewed.

The bibliographies of key articles, including previously published guidelines, were reviewed manually for relevant references. Additional MEDLINE searches were conducted to address specific issues that arose during development of the project, such as patient's age at endoscopy and gastric cancer rates, the role of NSAIDs in dyspepsia, and the diagnosis and treatment of gastroesophageal reflux disease (GERD). Because some of the most recent data were available only in abstract form, abstracts of the major gastroenterology meetings, such as the American Gastroenterological Association and the World Congress of Gastroenterology, were also reviewed.

The importance of costs and other economic considerations was recognized, and if appropriate economic data were available they were included. However, health economic data are limited in this area, particularly with respect to the Canadian health care system, and this review highlighted the need for more data to help guide management choices.

Relevant studies were graded to provide an indication of the strength of the evidence and the related recommendations. Diagnostic test studies were graded according to the rating used in the Report of the Canadian Hypertension Society Consensus Conference[3] (Appendix 1). All other key studies were graded using the levels of evidence and treatment recommendations of the Canadian Task Force on the Periodic Health Examination[4] (Appendix 2). Gaps in the existing evidence were identified, and where evidence was lacking, the best available evidence was considered and consensus sought.

Presentation of treatment recommendations in the clinical management tool

For each mini-management schema in the clinical management tool, treatment evidence was sought for 3 PPIs (lansoprazole, omeprazole and pantoprazole), 4 H_2-RAs (cimetidine, famotidine, nizatidine and ranitidine), cytoprotective agents (misoprostol only) and prokinetic agents (cisapride only). The treatment recommendations related to these compounds are listed by drug class (PPI for proton-pump inhibitors and H_2-RA for H_2-receptor antagonists) rather than by specific drug. If trial data are not available for all drugs in each category, footnotes are used to clarify the specific drugs and dosages for which evidence is currently available.

Background on dyspepsia

Terminology

Dyspepsia is a symptom complex rather than a specific disease. Most patients do not present to their physician complaining of "dyspepsia" but, instead, describe symptoms that the clinician interprets as dyspepsia.[5] These symptoms are subjective, and the patient's description may be language- and culture-dependent.[6,7] The variability of the physician's interpretation and of the patient's description has created confusion concerning a unifying definition of dyspepsia.[5] The term "dyspepsia" encompasses all relevant symptoms regardless of whether there is a demonstrable cause. However, for the purpose of the management tool, it is important to distinguish the terms dyspepsia, functional dyspepsia (dyspepsia for which investigation has shown no cause) and uninvestigated dyspepsia (dyspepsia for which no cause has yet been sought).

Dyspepsia

The CanDys Working Group agreed on the following working definition of dyspepsia: "Dyspepsia is a symptom complex of epigastric pain or discomfort thought to originate in the upper gastrointestinal tract, and it may include any of the following symptoms: heartburn, acid regurgitation, excessive burping/belching, increased abdominal bloating, nausea, feeling of abnormal or slow digestion, or early satiety." Dura-

Table 1: Summary of MEDLINE searches for treatment recommendations*

	Search terms; no. of citations within each mini-management schema			
	NSAID	GERD	*Hp* positive	*Hp* negative
Drug	Dyspepsia or ulcer + NSAID or aspirin or ASA	Reflux or gastroesophageal reflux disease	Dyspepsia + *Hp* infection or *Hp* positive	*Hp*-negative dyspepsia or functional dyspepsia or nonulcer dyspepsia
Proton-pump inhibitor	4	31	7	4
Lansoprazole	5	36	11	2
Omeprazole	31	166	39	19
Pantoprazole	1	12	4	1
H_2-blocker or H_2-receptor antagonist	9	37	–	4
Cimetidine	24	95	–	4
Famotidine	6	18	–	2
Nizatidine	4	10	–	1
Ranitidine	43	160	–	12
COX-2 inhibitor	25	–	–	–
Cisapride	–	40	–	25
Ranitidine bismuth citrate	–	–	4	–

Note: NSAID = nonsteroidal anti-inflammatory drug, ASA = acetylsalicylic acid, GERD = gastroesophageal reflux disease, *Hp* = *Helicobacter pylori*, COX = cyclo-oxygenase.
*MEDLINE searches for English-language clinical trials involving human subjects published from 1966 to October 1999.

tion was not specified as part of the definition because patients may present immediately following the onset of symptoms, or they may wait years before consulting their family physician.

Over the years, several definitions of dyspepsia have been proposed.[8–12] In 1991 an international panel of clinical investigators developed a comprehensive classification of functional gastrointestinal disorders, including dyspepsia, commonly referred to as the Rome Criteria.[13] The criteria were recently updated at the Rome II consensus conference,[14] and the following definition of dyspepsia was recommended: "Dyspepsia refers to pain or discomfort centred in the upper abdomen."

Dyspepsia can be caused by a variety of conditions. In a technical report of the American Gastroenterological Association, 36 original studies were reviewed in which patients with dyspepsia were investigated by means of endoscopy.[8] The 3 main organic causes of dyspeptic symptoms were duodenal or gastric ulcer (15% to 25% of cases), reflux esophagitis (5% to 15% of cases) and gastric or esophageal cancer (less than 2% of cases). More than 50% of patients with typical reflux symptoms, with pathological gastroesophageal reflux (e.g., diagnosed by means of 24-hour esophageal pH monitoring), have no macroscopic evidence of esophagitis and are classified as having endoscopy-negative reflux disease. The overall frequency of GERD is 20% to 40%. In Canada GERD is now more common than ulcers. Similarly, up to 60% of patients who present with dyspepsia will have no definite structural or biochemical explanation for their symptoms and are considered to have functional dyspepsia, often referred to in the literature as nonulcer dyspepsia.

Functional dyspepsia

At the Rome II consensus conference[14] the following definition for functional dyspepsia was recommended: "Twelve weeks or more (within the last 12 months) of persistent or recurrent dyspepsia and evidence that organic disease likely to explain the symptoms is absent (including at upper endoscopy)." In addition, 2 symptom subgroups for functional dyspepsia were proposed based on the predominant (or most bothersome) single symptom identified by the patient. For ulcer-like dyspepsia, pain centred in the upper abdomen is the most bothersome symptom. For dysmotility-like dyspepsia, an unpleasant or troublesome nonpainful sensation (discomfort) in the upper abdomen is the predominant symptom.

Uninvestigated dyspepsia

The Canadian clinical management tool developed by the CanDys Working Group begins with uninvestigated dyspepsia and is intended for the patient with new-onset or recurrent dyspeptic symptoms in whom no investigations have been conducted and no specific diagnosis for the current symptoms exists. Although the Rome II definition does not include reflux disease within dyspepsia, the CanDys Working Group felt strongly that this does not coincide with the conceptual framework that primary care physicians follow when a patient presents with uninvestigated dyspeptic symptoms. To be practical and reflect the reality of primary care, the consensus was that reflux disease is an integral constituent of uninvestigated dyspepsia. This is a major difference from the Rome II consensus guidelines and the American Gastroenterological Association medical position statement.[14,15] The difference reflects the needs of the primary care physician rather than those of the specialist and researcher.

Epidemiology and quality of life

Dyspepsia is a common condition. A recent study evaluating the prevalence of dyspepsia in the general population showed that 29% of all Canadians have substantial dyspeptic symptoms.[1] The reported prevalence of dyspepsia in Western countries generally ranges from 25% to 50%.[8-12,16-19] Much of the variability is likely the result of using different definitions, sampling methods or periods of surveillance.[17,20]

The natural history of dyspepsia is one of persisting or frequently recurring symptoms.[8,18,21,22] Although the overall prevalence of dyspepsia in a given community remains stable, symptoms will resolve in some people and develop in others.[16,17,19,23,24]

Few dyspepsia treatment trials have incorporated measures of quality of life,[25] but 2 recent studies from Canada[1] and Britain[26] investigated the effect of dyspeptic symptoms on quality of life in the general population. Both studies used the Psychological General Well Being Index as a measure and demonstrated that patients with dyspepsia have a significantly lower quality of life than do healthy subjects in the community. The quality of life of patients with dyspepsia is also lower than that of patients with peptic ulcer disease.[27]

Clinical management tool for uninvestigated dyspepsia

The clinical management tool maps a series of 5 key decision points with 4 related mini-management schemata (Figs. 1 to 5). The 5 key decision points (boxes A to E in Fig. 1) address the following questions: (A) Are there other possible causes for the symptoms? (B) Is the patient over 50 years of age, or does the patient have any alarm features? (C) Is the patient regularly using NSAIDs (including ASA)? (D) Is the dominant symptom heartburn or acid regurgitation, or both? (E) Is the patient infected with *H. pylori*?

The key decision points link directly to 4 related mini-

management schemata that include treatment recommendations for the following groups: (1) patients using NSAIDs, (2) patients with GERD, (3) patients with positive results of testing for *H. pylori* and (4) patients with negative results of testing for *H. pylori*. The treatment recommendations in each mini-management schema are ranked according to strength of evidence, and the schemata provide guidance for management until symptom resolution or referral for investigation.

The remainder of this document summarizes the evidence used to support each of the 5 key decision points related to diagnosis and investigation, followed by evidence for the treatment advice provided in the 4 related mini-management schemata. Each section is followed by a

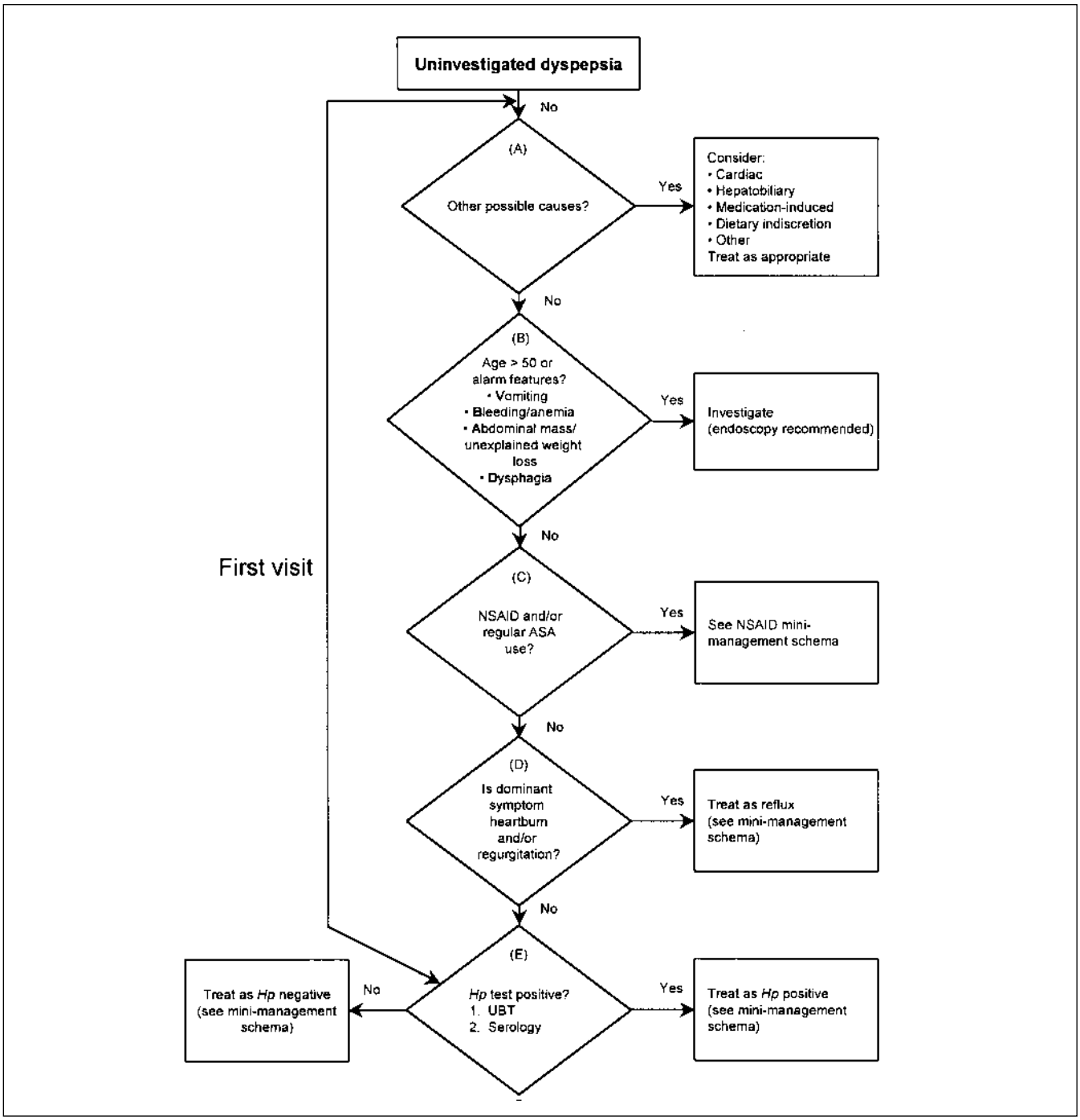

Fig. 1: Canadian clinical management tool for patients with uninvestigated dyspepsia in primary care. *Hp = Helicobacter pylori*, UBT = urea breath test. See Figs. 2–5 for the mini-management schemata.

graded recommendation, and the highest level of evidence available for each recommendation is indicated, with relevant references. Therapeutic choices are listed from most preferred to least preferred in each mini-management schema, based on available evidence of best clinical outcome.

Evidence related to the 5 key decision points: diagnosis and investigation

Identification of patients with other possible causes of dyspeptic symptoms or an increased risk of underlying structural abnormalities

Many patients with dyspeptic symptoms consult a physician because they fear serious disease,[28–30] including cancer[28,31] and heart disease.[28] The first priority of the primary care physician is to identify patients who have a higher risk of underlying structural abnormalities or other causes for their dyspeptic symptoms. Careful history-taking is crucial for the identification of these patients, and the first 3 key decision boxes in the clinical management tool outline the related recommendations (Fig.1). Although the decision boxes are mapped in a linear fashion for clarity of presentation, history-taking is not necessarily conducted in this sequence in clinical practice.

Box A: Other possible causes of symptoms

The clinician must consider the possibility that symptoms suggestive of dyspepsia may not originate from the upper gastrointestinal tract. A thorough history-taking and physical examination should identify patients for whom it is necessary to exclude cardiac, hepatobiliary and other nongastrointestinal origins of the presenting dyspeptic symptoms,[9] including possible medication-induced dyspepsia,[32] lifestyle or dietary indiscretions. Although it may be difficult to exclude all of these causes on history-taking, it is important to know when to investigate further.

Recommendation

Exclude other possible causes of the dyspeptic symptoms with thorough history-taking and physical examination. Consider cardiac and hepatobiliary sources as well as medication-induced symptoms, possible dietary indiscretions, lifestyle or other causes (grade C recommendation, consensus).

Box B: Older patients and patients with alarm features

Although cancer is a rare cause of dyspeptic symptoms (accounting for less than 2% of cases),[8] it is an important consideration. Alarm features and increased age identify patients with a higher risk of an organic cause for their uninvestigated dyspeptic symptoms, including cancer and ulcers.[33,34]

Retrospective studies indicate that most younger patients with gastric or esophageal cancer present with at least one alarm feature.[34,35] Unfortunately, if alarm features are present, the cancer is usually advanced, and curative resection is not possible.[35] This, however, does not diminish the importance of making the diagnosis.

Data from the United Kingdom suggest that cure rates for gastric cancer may be improved by early detection.[36,37] Prompt investigation in older patients with dyspeptic symptoms may increase the proportion of early gastric cancers that are detected and that potentially can be cured.[37] Four prevalence studies, assessing 5933 patients with dyspepsia, showed that gastric and esophageal cancers are rarely a cause of dyspeptic symptoms in younger patients.[33,34,37,38] In these studies, no cases of gastric or esophageal cancer were reported in any patient under 45 years of age.

The age threshold for a recommendation of prompt endoscopy in patients with uninvestigated dyspepsia should be driven in part by the incidence of gastric and esophageal cancer in the population in which one practises.[8,39–41] The American Gastroenterological Association's position statement recommended a cutoff age of 45 years for investigations.[15] The Canadian *Helicobacter pylori* Consensus Conference recommended an age threshold of 50 years for endoscopy in patients with new-onset dyspepsia[42] but provided no data to support their recommendation. Canadian statistics for the probability of the development of gastric cancer are presented by age in Table 2.[43] Both men and women have only a 0.1% probability of receiving a diagnosis of gastric cancer by age 50, but the probability increases with increasing age. Incidence rates of esophageal cancer also increase with increasing age but are lower than those of gastric cancer. The incidence rates of various cancers in Canada and the United States are similar.[43] The following esophageal cancer rates per 100 000 have been reported for the United States: 1.1 for people aged 40 to 44 years, 2.7 for those aged 45 to 49, 5.6 for those aged 50 to 54, and 10.2 for those aged 55 to 59.[44]

Another important aspect of prompt investigation is that normal findings on endoscopy can provide reassurance for both the patient[45–47] and the physician. It was the consensus of the CanDys Working Group that 50 years is a reasonable cutoff age for prompt investigation in patients with uninvestigated dyspepsia.[41] A referral for further investigation is always based on clinical judgement. For example, when assessing a patient who presents with dominant heartburn symptoms, the patient with stable symptoms responsive to antacids for many years must be considered differently from the older patient with recent onset of heartburn.

There are no prospective studies evaluating the value of alarm features. There is consensus in the literature that the presence of alarm features warrants prompt investigation. The acronym "VBAD" can serve as a memory cue for these alarm features, which include (persistent) **v**omiting, evidence of gastrointestinal **b**leeding or anemia, **a**bdominal mass or unexplained weight loss, and **d**ysphagia.

Diagnostic test: endoscopy or radiography? Barium meal studies are commonly used by Canadian family physicians for investigating dyspepsia.[2] However, it has repeatedly been shown that endoscopy is superior to radiography of the upper gastrointestinal tract for the diagnosis of organic causes of dyspepsia.[8,48–52] Although the sensitivity (proportion of true-positive results) and specificity (proportion of true-negative results) of radiography varied between studies, in a study directly comparing double-contrast barium meal and endoscopy a diagnostic accuracy of 70% was reported for radiography, compared with 96% for endoscopy ($p < 0.001$).[49]

The choice of test may vary according to where one practises, and clinical judgement must be applied in each case. The time it takes to get a referral to a gastroenterologist or to have endoscopy of the upper gastrointestinal tract performed may influence the decision as to which test is ordered.[2] Furthermore, a normal x-ray film will provide reassurance to the physician and patient that a serious cause for the dyspepsia symptoms is less likely.

Recommendations

Prompt investigation is recommended for patients over 50 years of age with uninvestigated dyspepsia and for any patient presenting with alarm features. Alarm features include persistent vomiting, evidence of gastrointestinal bleeding or anemia, presence of an abdominal mass or unexplained weight loss, and dysphagia (grade B recommendation, level III evidence[33,34,37,43]).

Endoscopy is the recommended method of investigation for patients with uninvestigated dyspepsia who are over 50 years of age or who have alarm features (grade A recommendation, level II evidence[8]).

Box C: Patients who use NSAIDs

Chronic use of a conventional NSAID, including ASA, is associated with an increased frequency of gastric and duodenal ulcers. Endoscopic studies indicate that the prevalence of peptic ulcers in people who use NSAIDs regularly is between 10% and 30%.[53,54] A meta-analysis showed that users of NSAIDs have approximately a 3 times greater relative risk for the development of serious adverse gastrointestinal events than nonusers.[55] There are differences among NSAIDs in the frequency with which they cause peptic ulcers.[56,57] Although *H. pylori* infection is clearly the most common cause of peptic ulcers, NSAIDs are responsible for most *H. pylori*-negative ulcers.[58–61] It is unclear whether there is synergy between *H. pylori* and NSAIDs in causing ulcer. Any interaction is likely to be small.[62,63]

COX-2 inhibitors have recently become available and appear to have a safer gastrointestinal profile than conventional NSAIDs.[64] Their development is based on the notion that the COX-1 enzyme predominates in the stomach, producing protective prostaglandins in the gastric mucosa. In contrast, the COX-2 enzyme is preferentially induced by inflammation, leading to pain and swelling. Although in reality the balance between COX-1 and COX-2 production is more complex, there is strong evidence that the COX-2 inhibitors have fewer side effects, such as gastric and duodenal ulcers and possibly dyspepsia, than conventional NSAIDs.[64–70]

Although most physicians believe that both ASA and non-ASA NSAIDs lead to dyspeptic symptoms, the actual data are controversial, especially in younger patients. When ASA use was assessed as a potential risk factor for dyspepsia in subjects less than 65 years of age with uninvestigated dyspepsia, two studies did not show a significant association.[71,72] One subsequent study did demonstrate a significant association between dyspepsia and ASA intake, but a dose–response curve could not be detected.[73] The data showing that non-ASA NSAIDs cause dyspepsia are not consistent.[72,73] However, a recent meta-analysis, available at present only in abstract form, indicates that NSAIDs are clearly associated with dyspepsia.[74] Studies of the prevention of NSAID-related ulcers showed that acid suppression lowers the frequency of ulcers and reduces dyspepsia

Table 2: Probability of the development of gastric cancer for men and women in Canada by age*

	Age, yr; probability, %						
Sex	30	40	50	60	70	80	90
Men	–	–	0.1	0.2	0.6	1.1	1.4
Women	–	–	0.1	0.1	0.3	0.6	0.8

*Adapted from reference 43. The probability of the development of cancer was calculated based on age- and sex-specific cancer incidence and death rates for Canada in 1993 and on life tables based on all-cause death rates for 1992–1994.

symptoms in the absence of an active ulcer.[75,76] The data on COX-2 inhibitors also suggest that patients taking these drugs have a slightly lower frequency of dyspepsia than those taking conventional NSAIDs.[67,68]

Few trial data are available to assess whether NSAID use is predictive of organic disease in patients with dyspepsia, especially in those aged 50 years or less. One study, involving 109 patients with arthritis who had been taking NSAIDs in therapeutic dosages for at least 4 weeks, showed that upper abdominal complaints were an independent predictor of ulceration.[75] The report did not provide data for young versus older patients, although the demographic characteristics of the study participants indicated that 75% were over 45. In a retrospective UK study assessing 8156 patients, no difference was found in the prevalence of endoscopic abnormalities between patients who used ASA or other NSAIDs and nonusers.[76] The applicability of these data to patients aged 50 years or less who present with uninvestigated dyspeptic symptoms is unknown. Despite the lack of definitive data, there was consensus among the CanDys Working Group members that NSAIDs, including ASA, should be considered as potential causes of dyspepsia. If there are no alarm features, investigation is not warranted. The first step in management is to stop the NSAID use if possible and to determine whether the patient's condition subsequently improves.

Recommendation

Patients with uninvestigated dyspepsia who are regular users of NSAIDs (including ASA) should be identified, and if there are no alarm features, they can be managed without initial endoscopy (grade C recommendation, consensus).

Differential diagnosis of uninvestigated dyspepsia in patients aged 50 years or less with no alarm features

The division of dyspepsia into subgroups, based on clusters of symptoms, was first proposed in 1988.[77] The subgroups ulcer-like, reflux-like and dysmotility-like dyspepsia were intuitively attractive because they coincide with beliefs about the cause of symptoms: acid for ulcer-like and reflux-like dyspepsia, and motility abnormalities for dysmotility-like dyspepsia. It was initially considered that subclassification had the potential to guide the choice of treatment.[77,78] However, the usefulness of subclassification has not been evaluated in light of the knowledge that most ulcer disease is attributable to *H. pylori* infection or NSAID use. Symptom subgroups have subsequently been found to have a poor predictive value for endoscopic diagnosis.[31,79,80] Furthermore, several studies have shown considerable overlap between the subgroups, both for patients with uninvestigated dyspepsia and for those with functional dyspepsia.[17,29,31,38,80–83] In a recent study assessing the value of clinical judgement in predicting the endoscopic diagnosis in patients with uninvestigated dyspepsia, the overall accuracy of clinical diagnosis was only 57%.[84] In addition, one-third of patients with a major endoscopic finding, such as ulcers, were misclassified as having functional dyspepsia.

Box D: Identification of patients with dominant symptom of heartburn or acid regurgitation, or both

Although symptom clusters have generally proven to be poor predictors in the differential diagnosis of dyspepsia, Klauser and colleagues[85] found that when heartburn or acid regurgitation are dominant symptoms, they have a high specificity (89% and 95% respectively) for GERD. The presence of heartburn or acid regurgitation as dominant symptoms is now widely recognized as a reliable indicator that a patient has GERD.[8,13,86–88] A study conducted in the primary care setting of 3 European countries assessed the clinical features and endoscopic diagnoses in patients presenting with GERD.[89] The results demonstrated that primary care physicians were able to diagnose GERD accurately based on dominant symptoms. This finding supports the approach that initial treatment can be started based on symptoms of reflux in primary care.

An important point for the diagnosis of GERD is that most affected patients do not have macroscopic esophagitis.[8,90–94] These patients are considered to have endoscopy-negative reflux disease. Endoscopy is therefore not a useful diagnostic "gold standard" for GERD, nor is 24-hour pH monitoring.[90–99]

A reliable interpretation of the term "heartburn" is key for the diagnosis of GERD.[99,100] The term is often misinterpreted by patients and described as "pain or discomfort in the stomach."[87] If heartburn is described as a sensation of "a burning feeling rising from the stomach or lower chest toward the neck," patient recognition is higher.[87] Furthermore, this definition predicted the response to treatment with antisecretory agents.[87]

Recommendations

Patients aged 50 years or less with uninvestigated dyspepsia and dominant symptoms of heartburn or acid regurgitation, or both, should be diagnosed as having GERD and be treated accordingly (grade B recommendation, level II-2 evidence[85,87,90–94]).

Rather than using the term "heartburn," describing the sensation of "a burning feeling rising from your stomach or lower chest toward your neck" increases the diagnostic accuracy for GERD (grade B recommendation, level II-2 evidence[87]).

Box E: Helicobacter pylori *"test-and-treat" strategy for patients with uninvestigated dyspepsia without alarm features*

There is little doubt that the isolation of *H. pylori* is one of the most important medical discoveries in the last 20 years. Treatment of infection with this organism has revolutionized the management of duodenal and gastric ulcer disease.[101] *H. pylori* infection is associated with 90% to 95% of duodenal ulcers[88,101] and 60% to 80% of gastric ulcers.[60,61,88] A systematic review of the literature disclosed moderate epidemiologic evidence for an association between chronic *H. pylori* infection and gastric cancer.[102] The International Agency for Research on Cancer[103] has classified *H. pylori* as a group I (definite) carcinogen in humans. However, development of gastric cancer is a multifactorial process that includes other factors, such as a diet low in vitamin C or high in salt, and smoking. As mentioned, the lifetime risk for gastric cancer is low in Canada,[43] and the incidence has gradually decreased over the last 40 years.

Currently, there is uncertainty as to whether *H. pylori* plays a role in dyspepsia in the absence of ulcers. Four separate reviews have evaluated whether there is an association between *H. pylori* and functional dyspepsia,[102,104–106] and none reached a definitive conclusion. Five recent randomized placebo-controlled trials assessing the value of therapy to eradicate *H. pylori* in patients with functional dyspepsia produced conflicting results: 3 studies showed no significant reduction of dyspeptic symptoms after 1 year,[107–109] and 2 showed that eradication of the organism did resolve symptoms in 25% to 30% of patients.[110,111] One explanation for the 2 studies with positive results is that they were conducted in Scotland and Ireland, both countries with a high prevalence of peptic ulcer disease.

The distinction between functional (investigated) and uninvestigated dyspepsia is relevant when a noninvasive *H. pylori* test-and-treat strategy is considered. Among patients with uninvestigated dyspepsia who harbour *H. pylori*, there will be a proportion (estimated at 5% to 15%) with peptic ulcer disease; these patients will benefit from eradication of the organism. Perhaps some patients in whom gastric cancer will ultimately develop will also benefit from eradication of *H. pylori*, although there are no clinical trial data to prove this hypothesis. Despite the lack of direct evidence for prevention of gastric cancer, this is a consideration when a decision regarding treatment of *H. pylori* infection is made.

The main options for the treatment of younger patients with uninvestigated dyspepsia who have no alarm features include the following: (1) a trial of empiric (antisecretory or prokinetic) therapy (*other* than *H. pylori*-eradication therapy), with investigation reserved for symptomatic failures; (2) diagnostic evaluation (preferably endoscopy) for all, with treatment based on the findings of the diagnostic test; (3) noninvasive testing for *H. pylori* followed by eradication therapy for patients with positive results ("test-and-treat"); and (4) noninvasive testing for *H. pylori* followed by endoscopy for patients with positive results.[15] The last option is based on the assumption that *H. pylori* infection should be treated only if it has led to macroscopic disease, such as ulcer. Data from randomized clinical trials comparing some of these strategies are just emerging, but it should also be noted that the Canadian *Helicobacter pylori* Consensus Conference recommended that eradication therapy be offered to all patients with a positive result of testing for *H. pylori*.[112]

A prospective randomized study assessing patients with uninvestigated dyspepsia showed that a strategy of empiric H_2-blocker therapy was associated with lower patient satisfaction and higher costs than a strategy of prompt endoscopy,[113] although at 1 year there were no differences between the 2 groups in overall severity of dyspeptic symptoms or improvement in quality of life. A more recent randomized controlled trial involving patients with persistent dyspeptic symptoms demonstrated that empiric treatment with a PPI resulted in 69% fewer diagnostic endoscopy procedures, lower medical costs and equal effectiveness in the first year compared with a strategy of prompt endoscopy.[114]

Two recent randomized trials conducted in primary care settings compared a strategy of prompt endoscopy with a test-and-treat strategy. Lassen and associates[115] reported that the test-and-treat strategy was highly cost-effective after 1 year of follow-up. There were no differences in severity of dyspeptic symptoms between the strategies, and the number of endoscopy procedures was reduced by 63% in the test-and-treat group. The prompt-endoscopy group, however, reported greater satisfaction with their treatment. Jones and coworkers[116] also reported that, at 1 year, the test-and treat strategy resulted in a significant reduction in the number of endoscopy procedures and substantially reduced costs compared with a strategy of prompt endoscopy. In another randomized trial, among patients less than 45 years of age with dyspepsia who harboured *H. pylori*, empiric anti-*H. pylori* therapy reduced dyspepsia severity scores and increased the scores for several measures of quality of life more than a strategy of endoscopy with subsequent treatment based on the results of the procedure.[117] Results from other studies also support the cost-effectiveness of the *H. pylori* test-and-treat strategy.[118–120]

Decision analysis models comparing the cost-effectiveness of various strategies suggest that a noninvasive test-and-treat strategy would reduce the endoscopy workload and be cost-effective.[121–123] A recent Canadian analysis model that used Canadian data on health care costs also suggested that empirically based management strategies for patients under 45 years of age with uninvestigated dyspepsia are cost-effective compared with endoscopy or barium investigation.[124] Another model suggested that a strategy based on urea breath testing (UBT) in the same patient population is more cost-effective than empiric antisecre-

tory therapy.[125] The first randomized controlled Canadian trial of a noninvasive *H. pylori* test-and-treat strategy in patients with uninvestigated dyspepsia in primary care has just been completed.[126] It showed a 14% benefit in favour of *H. pylori* treatment over placebo (50% v. 36%), thus supporting the test-and-treat strategy.

The feasibility of the various management options in the Canadian primary care setting is influenced by the time it takes for the patient to be seen by a gastroenterologist after a referral has been made, the availability and waiting times for endoscopy and the availability of noninvasive tests for *H. pylori*. In a recent survey of Canadian family physicians, 70% of the respondents indicated that the estimated mean delay of 5 weeks for a gastrointestinal referral adversely influenced their decision to refer patients.[2]

Family physicians have serologic testing and UBT available as noninvasive tests. The carbon-14 (radioactive) UBT is available only in a few large urban centres. However, the carbon-13 (nonradioactive, stable) UBT is becoming increasingly available. Unfortunately, for both carbon-13 and carbon-14 UBTs the cost is not as yet reimbursed by provincial health ministries or most insurance companies, despite the recommendation of the Canadian *Helicobacter pylori* Consensus Conference that it is the preferred noninvasive test for *H. pylori*.[112] Most general practitioners in Canada have access only to serologic testing for the diagnosis of *H. pylori* infection. There is evidence that a negative *H. pylori* test result may provide as much reassurance for patients as a normal result of endoscopy.[127,128] This is discussed further in the section "Testing for *H. pylori* infection."

In deciding on a noninvasive *H. pylori* test-and-treat strategy in patients with uninvestigated dyspepsia, it is necessary to consider both the potential benefits and the drawbacks. There are several arguments in favour of a test-and-treat option. First, some patients with functional dyspepsia may benefit; the overall magnitude of benefit remains controversial but is likely under 20%.[106–110] Second, patients with undiagnosed duodenal and gastric ulcers will benefit. The estimated lifetime prevalence of peptic ulcer disease in the general population is 5% to 15%.[129] Third, eradication may halt the progression from chronic gastritis to gastric cancer and hence prevent this cancer. Although there are no data from longitudinal studies to support this hypothesis, results from a modelling study[130] and a nonrandomized Japanese study[131] suggest this may be the case in selected patient populations. Finally, there is a strong desire among many patients to undergo testing and be treated for *H. pylori* infection, as public awareness of the infection and its consequences is high. This is not in itself a reason to test for *H. pylori* infection, but symptoms alone are inadequate to exclude this diagnosis in a patient with dyspepsia.

Recommendation

A test-and-treat strategy for uninvestigated dyspepsia in younger patients (aged 50 years or less) who have no alarm features is recommended (grade B recommendation, level I evidence[115–117]).

Testing for* H. pylori *infection: Recent guidelines from the Canadian *Helicobacter pylori* Consensus Conference include an overview of diagnostic tests for the detection of *H. pylori* infection.[42] Infection can be detected by invasive (endoscopy based) or noninvasive (UBT or serologic testing) diagnostic tests. For serologic testing, both laboratory (serum) and office-based (whole blood) tests are available.[20] Because different commercial and noncommercial serologic assays are available, it is important that they be validated locally.[42]

Comparison of serologic testing and UBT has shown the latter to be consistently superior for the diagnosis of *H. pylori* infection.[132–138] *An important difference between UBT and serologic testing is that the latter cannot be used to determine cure*, as the IgG antibodies against *H. pylori* remain detectable for a long time (6 to 12 months) after eradication of the organism.[139–141]

In the interpretation of a diagnostic test, the positive and negative predictive values are the most important. In contrast to the sensitivity and specificity of the test, the positive and negative predictive values are influenced by the prevalence of the disease one wants to diagnose. In Canada the overall prevalence of *H. pylori* infection is estimated to be 30% to 40% and increases with increasing age (8% increase per decade).[142] The prevalence is higher among patients with a lower socioeconomic status and probably also among immigrants from countries where *H. pylori* infection is endemic.[143,144]

Calculation of positive and negative predictive values using the mean sensitivity and specificity values from a meta-analysis of serologic testing[136] and Canadian data on the prevalence of *H. pylori* infection[142] shows that serologic testing has a high negative predictive value (90%) in young patients (Table 3). A younger patient is therefore unlikely to be infected with *H. pylori* if the test result is negative. In contrast, below the age of 50 years, the positive predictive value ranges from 52% to 72%, which indicates that false-positive results do occur. UBT has a high positive predictive value and negative predictive value (both greater than 90%), even in groups with a low prevalence of *H. pylori* infection. Therefore, it is the preferred test.[146] However, UBT is currently not widely available for primary care physicians in Canada. If neither UBT nor serologic testing is available, endoscopy plus gastric biopsy is an alternative method to assess *H. pylori* status.

Recommendation
Noninvasive methods are recommended for the detection of *H. pylori* in patients aged 50 years or less with uninvestigated dyspepsia who have no alarm features. UBT is the preferred test, and a locally validated serologic test is considered a second option (grade B recommendation, level II-2 evidence[132,134–138]).

Evidence related to the 4 mini-management schemata

Management of patients who use NSAIDs

There is consensus that NSAIDs can cause dyspeptic symptoms.[74] The evidence is less compelling for patients who use ASA regularly (i.e., daily). However, since even low-dose ASA can lead to ulcer formation, it seems likely that ASA may sometimes cause dyspepsia. If possible, NSAID use should be stopped and the patient's response monitored closely.[58] If the patient must continue with NSAID therapy (including ASA) or if symptoms have not resolved after NSAID therapy is stopped, the patient should be treated empirically or referred for investigation.

Ulcer prevention is an important consideration in patients taking NSAIDs. Randomized placebo-controlled trials of at least 2 months' duration have shown that treatment with misoprostol (600 to 800 μg/d),[147,148] high doses of famotidine (40 mg twice daily)[149] and omeprazole (20 mg once daily)[150,151] provide effective prophylaxis against NSAID-related peptic ulcer in patients receiving long-term NSAID therapy. In addition to famotidine, other H_2-RAs have been studied for the prevention of NSAID-induced ulcers. Randomized placebo-controlled studies have shown that ulcer occurrence with nizatidine treatment (150 mg twice daily) was not statistically different from that with placebo,[152] whereas therapy with ranitidine at a standard dosage (150 mg twice daily)[153,154] and at 300 mg twice daily[155] was protective against duodenal ulcer but not against gastric ulcer in long-term NSAID users. A randomized study comparing misoprostol (200 μg 4 times daily) and ranitidine (150 mg twice daily) demonstrated that misoprostol was more effective than ranitidine in preventing NSAID-induced gastric ulcers, but the 2 medications had comparable efficacy in the prevention of NSAID-induced duodenal ulcers.[156]

Randomized controlled trials that assessed both healing and prevention of ulcers associated with NSAID use have demonstrated the effectiveness of high-dose famotidine therapy (40 mg twice daily) compared with placebo[157] and the superiority of omeprazole (20 or 40 mg once daily) compared with misoprostol (200 μg 4 times daily)[158] and ranitidine (150 mg twice daily).[159] Another recent study showed that lansoprazole (15 or 30 mg/d) was significantly better than ranitidine (150 mg twice daily) in healing NSAID-induced gastric ulcers in patients who continued to take these agents.[160] Data on the prevention of NSAID-related ulceration are not yet available for pantoprazole and lansoprazole.

The COX-2 inhibitors celecoxib and rofecoxib have been shown to be much safer than conventional NSAIDs, causing fewer gastric and duodenal ulcers and upper gastrointestinal tract symptoms.[60,74] To date, these drugs have been studied only in acute pain syndromes and in patients with rheumatoid arthritis or osteoarthritis.[65–69] Intuitively, it seems reasonable to change from a conventional NSAID to a COX-2 inhibitor in patients with dyspeptic symptoms associated with NSAID use since COX-2 inhibitor therapy produces a lower rate of dyspepsia and ulcer-related complications. However, this strategy has not been tested specifically in a patient population with symptoms or complications from NSAID therapy, and the evidence for a change is therefore anecdotal at best. Furthermore, there is experimental evidence in animals that COX-2 inhibitors may delay ulcer healing.[161,162] There must therefore be reservations about a change from NSAIDs to COX-2 inhibitors in patients with uninvestigated dyspepsia who may have undiagnosed ulceration.

Because none of the NSAID studies included patients

Table 3: Positive and negative predictive values for the detection of *H. pylori* through serologic testing in Canadians by age*

Age, yr	Prevalence of *H. pylori* infection, %	Positive predictive value, %	Negative predictive value, %	False-positive result, %	False-negative result, %
20–29	21	52	95	48	5
30–39	28	61	93	39	7
40–49	39	72	89	28	11
50–59	41	74	88	26	12
60–69	47	78	86	22	14

*Calculated using meta-analysis data for serologic testing (sensitivity 85% and specificity 79%)[133] and 1994 Canadian data on the prevalence of *H. pylori* infection[142] according to Lang and Secic.[145]

aged 50 years or less with uninvestigated dyspepsia, they are not directly applicable to this mini-management schema. Most of the studies reviewed by the group focused on ulcer prevention and ulcer healing. However, only studies evaluating omeprazole also showed benefit for dyspeptic symptoms compared with misoprostol and ranitidine.[158,159] Although several of the studies were level I randomized controlled trials for healing and prevention of ulcers, only grade C recommendations can be made for dyspepsia. There are also data on high-dose famotidine therapy (40 mg twice daily) showing a preventive effect on ulcer formation. A single study assessing ranitidine (300 mg twice daily) showed prevention of duodenal ulcers but not of gastric ulcers. Clearly, more studies are needed in this area.

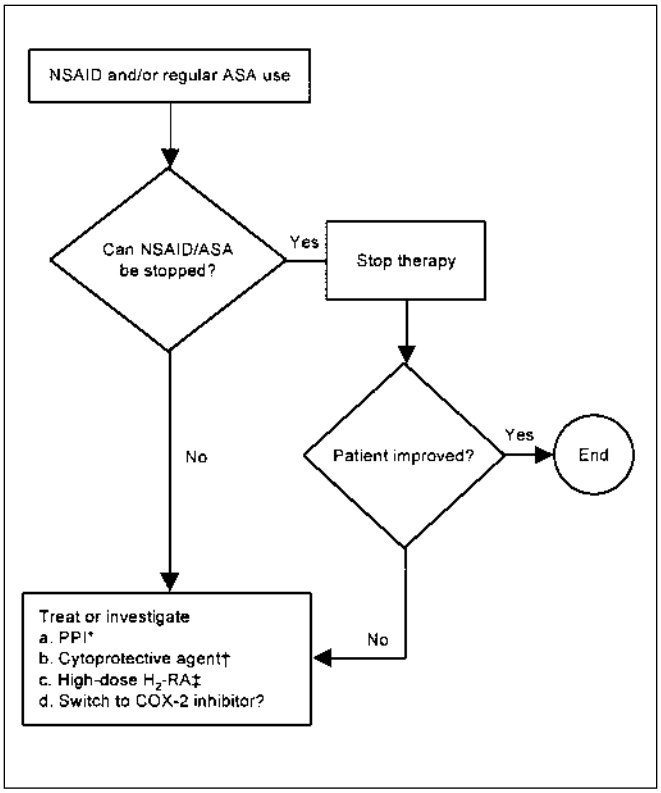

Fig. 2: NSAID mini-management schema. PPI = proton-pump inhibitor, H_2-RA = H_2-receptor antagonist, COX = cyclooxygenase.
***Most of the data in this area are for omeprazole (20 or 40 mg once daily) in NSAID-induced duodenal and gastric ulcers. Lansoprazole (15 or 30 mg once daily) has been shown to be significantly better than ranitidine in the healing of acute NSAID-induced gastric ulcers. There are no data for pantoprazole.**
†Data for misoprostol only.
‡There are data only for high-dose famotidine (40 mg twice daily). Ranitidine (300 mg twice daily) did prevent duodenal but not gastric ulcers in a small study.

Recommendations
If possible, NSAID use should be stopped and the patient's response monitored (grade C recommendation, level III evidence). If NSAIDs cannot be stopped the choice is to treat or investigate.

Treatment recommendations for patients aged 50 years or less who present with uninvestigated dyspepsia, who have no alarm features and who need to use NSAIDs (including ASA) are as follows:

(a) PPI (grade C recommendation, consensus).
(b) Cytoprotective agent (grade C recommendation, consensus) .
(c) High-dose H_2-RA therapy (grade C recommendation, consensus).
(d) Consider switch to COX-2 inhibitor (grade C recommendation, consensus)?

Management of patients with gastroesophageal reflux disease

Patients aged 50 years or less with uninvestigated dyspepsia who have dominant symptoms of heartburn or acid regurgitation, or both, should be managed as patients with GERD. The treatment goal is symptom relief. Five treatment possibilities for GERD were assessed: lifestyle modification, antacids, H_2-RAs, prokinetics and PPIs.

Although the CanDys Working Group recognizes that lifestyle modifications are commonly recommended for patients with GERD, there are sparse controlled data available. Most studies assessing lifestyle modification involved patients with moderate or severe GERD. Elevation of the head of the bed failed to decrease the frequency of reflux episodes significantly in 2 studies,[163,164] but it reduced symptoms and improved endoscopic appearance in patients with severe esophagitis in another study.[165] The authors of a more recent work found that gastroesophageal reflux in obese patients did not abate after weight reduction.[166] Clinical experience suggests that patients with milder symptoms of GERD may derive benefit from lifestyle modification.

In a review of lifestyle modification and medical therapy with antacids in GERD, Kitchin and Castell[167] concluded that definitive evidence of efficacy is unavailable because of the lack of well-controlled trials. The review included several studies assessing the efficacy of antacids versus placebo. Three of these studies showed comparable efficacy for antacids and placebo,[168–170] and 2 studies showed that antacids provided benefit compared with placebo.[171,172]

A recent meta-analysis of 43 randomized studies involving adults with endoscopically proven erosive esophagitis (grade II to IV GERD) showed that more complete esophageal healing and heartburn relief was obtained with PPIs than with H_2-RAs.[173] In addition, the speed of healing

and symptom relief was nearly twice as fast with PPIs. However, these studies were restricted to patients with more severe disease than that of the average patient who presents in primary care with symptoms of milder GERD.[174] The meta-analysis included studies using lansoprazole, omeprazole and pantoprazole.

As noted previously, most patients with GERD will not have esophagitis but will have endoscopy-negative reflux disease. PPIs have been reported to be superior as initial treatment in these patients.[92,93,175] A 4-week study in a general practice setting demonstrated that omeprazole (20 mg once daily) produced a significantly higher rate of symptom relief than ranitidine (150 mg twice daily) among patients with GERD (61% v. 40%).[94] Similarly, in another 4-week randomized study, heartburn was resolved in significantly more patients treated with omeprazole (20 mg once daily) than in those who received cisapride (10 mg four times daily) (65% v. 41%).[91] Symptom relief was comparable in patients with or without endoscopic evidence of erosive esophagitis.

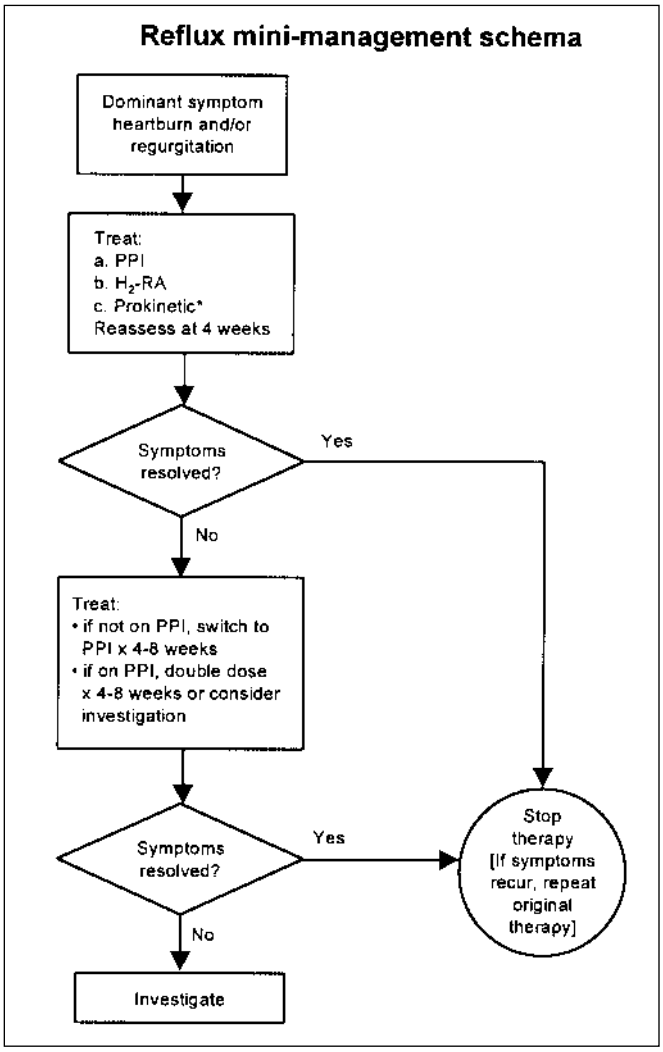

Fig. 3: Reflux mini-management schema.
***Data for cisapride only. There are reported adverse cardiac events related to the use of cisapride, and sometimes this can result in serious ventricular arrhythmias and possibly death. This must be taken into consideration before prescribing cisapride.**

The evidence indicates that PPIs are also superior for endoscopy-negative reflux disease. Most data to date are for omeprazole, but studies with lansoprazole and pantoprazole are emerging.[176,177]

A recent analysis of the efficacy of prokinetic therapy for GERD revealed that cisapride is the only prokinetic agent that can be recommended.[178] The analysis included 4 placebo-controlled studies showing that cisapride produced significantly higher healing rates than placebo among patients with mild to moderate esophagitis.[179–182] Six additional studies demonstrated that cisapride and H_2-RA therapy produced similar healing rates.[183–188] The combination of cisapride with either an H_2-RA[189,190] or omeprazole[191] did not produce an additional benefit in healing after 6 to 8 weeks of therapy. Furthermore, among 11 placebo-controlled studies evaluating resolution of reflux symptoms, cisapride produced greater symptom relief than placebo in 10 studies and comparable relief to placebo in 1 study.[178] The symptom relief seen with cisapride (39%) was comparable to that with H_2-RAs (32%) in 6 studies.[178] Comparison of the results from studies of therapy for endoscopy-negative reflux disease also support the notion that cisapride and H_2-RAs produce comparable relief of reflux symptoms.[91–94,192] However, both treatments produced significantly lower rates of complete symptom relief than omeprazole.[91,193,194] Concerns have been raised both in Canada and in the United States about potentially serious cardiac side effects associated with cisapride.[195,196] The side effects include prolongation of the Q–T interval, ventricular tachycardia and death. Interactions can occur with other medications, such as antiarrhythmics, antidepressants and antihistamines.

There is a progressive increase in the proportion of patients who become symptom-free as the duration of therapy increases, regardless of the type of therapy; however, the proportion of patients who become symptom-free each week is highest during the first 2 to 4 weeks of therapy, and the rate of relief is greatest among patients receiving PPIs.[91,173] Most patients who will become symptom-free with PPI therapy will have done so by 4 weeks, and those who have not responded to treatment with H_2-RAs or cisapride by 4 weeks are less likely to respond to another 4 to 8 weeks of therapy. Thus, reassessment of the patient after 4 weeks of therapy is reasonable.

Although the efficacy of a standard-dose H_2-RA and of cisapride is essentially equivalent, the former is preferred because of the potential adverse events associated with cisapride therapy.[197]

Currently, there is debate as to whether a step-up ap-

proach (start with H_2-RA and switch to PPI if no response) or a step-down approach (start with PPI and switch to H_2-RA if the patient responds) is better.[193] Studies in primary care that enrolled patients with reflux symptoms showed that the severity of heartburn and the duration of symptoms were similar in patients who were subsequently identified as having endoscopy-positive GERD (esophagitis) or endoscopy-negative GERD.[198] The implication is that neither the severity of disease nor the duration of symptoms is a reliable predictor of treatment response. The data clearly show that PPIs are superior to H_2-RAs and cisapride. PPIs provide more rapid and more complete relief of symptoms and, if erosive lesions are present, higher rates of healing of the esophagitis.

In the recommendations, PPIs are listed as first choice over H_2-RAs based on efficacy data. Few studies directly compared the various PPIs or H_2-RAs with each other. However, because healing rates and data on symptom relief are similar within each drug class, the class is listed rather than individual compounds. The current uncertainty regarding the step-up and step-down approaches is driven mainly by cost considerations. Therefore, the initial approach to management should be determined by the physician's assessment of the patient's clinical needs and the cost of medications.

Recommendations

The effectiveness of lifestyle modifications and antacids for the treatment of GERD is not proven. Patients with mild GERD symptoms may derive benefit from these treatments (grade C recommendation, consensus).

Treatment recommendations for patients with a dominant symptom of heartburn or acid regurgitation, or both, are as follows:

(a) PPI (grade A recommendation, level I evidence[91,94]).
(b) H_2-RA (grade A recommendation, level I evidence[178]).
(c) Prokinetic agent (grade A recommendation, level I evidence[178]).

Patients should be reassessed after 4 weeks of therapy (grade C recommendation, consensus).

Management of patients with a positive result of testing for *Helicobacter pylori*

H. pylori eradication therapy is the standard of care for all patients with duodenal or gastric ulcers who have been shown to harbour the organism.[58,199–201] Because of the compelling evidence that *H. pylori* is a true pathogen, there is an increasing consensus worldwide to treat all patients with positive results of testing for *H. pylori*.[42]

Helicobacter pylori *eradication therapy*

In accordance with the recommendations of the Canadian *Helicobacter pylori* Consensus Conference, first-line eradication therapies for *H. pylori* are triple therapies of a PPI plus 1000 mg of amoxicillin plus 500 mg of clarithromycin (PPI + AC), or a PPI plus 500 mg of metronidazole plus 250 or 500 mg of clarithromycin (PPI + MC), twice daily for 1 week; or ranitidine bismuth citrate plus either AC or MC.[42] These triple therapies achieve eradication

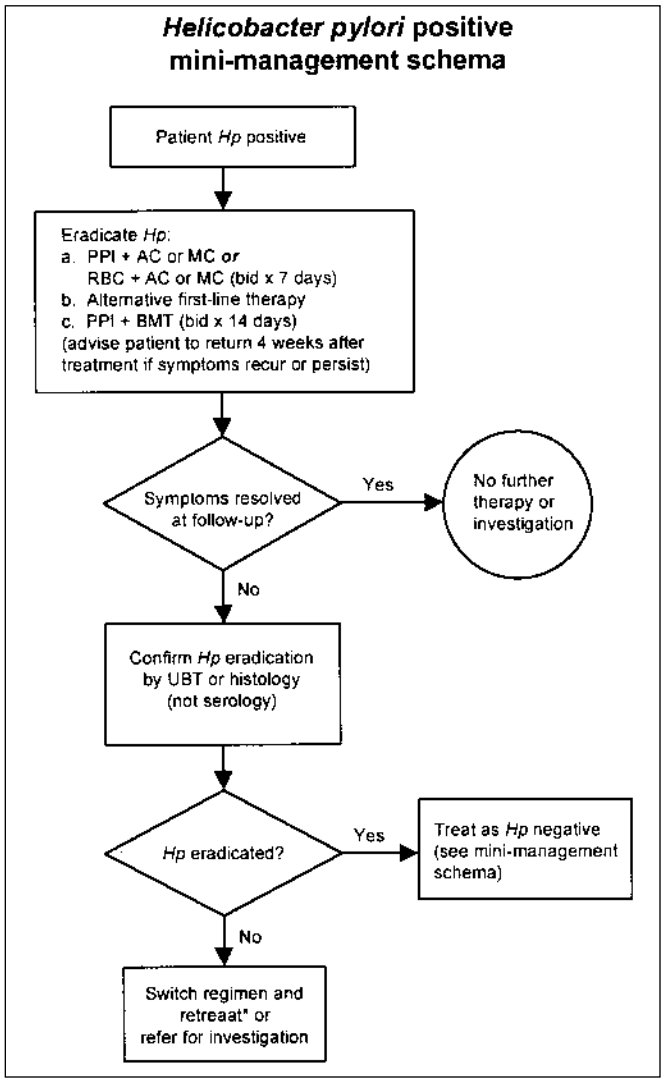

Fig. 4: *Helicobacter pylori*-positive mini-management schema. A = amoxicillin 1000 mg; B = bismuth subsalicylate (2 tablets); C = clarithromycin 250 or 500 mg (500 mg if treatment failure); M = metronidazole 500 mg (250 mg in BMT [bismuth–metronidazole–tetracycline) combination therapy; PPI = lansoprazole 30 mg, omeprazole 20 mg or pantoprazole 40 mg; RBC = ranitidine bismuth citrate 400 mg; T = tetracycline 500 mg. *If PPI or RBC + MC (metronidazole + clarithromycin) was used, switch to PPI or RBC + AC (amoxicillin + clarithromycin) and vice versa, or switch to a 14-day course of PPI + BMT.

rates of about 85% to 90%. For the PPI-based therapies, lansoprazole, omeprazole or pantoprazole can be used.

If the first eradication therapy has failed, the action recommended by the Canadian *Helicobacter pylori* Consensus Conference is to use a different first-line therapy than that used initially (e.g., switch from PPI + AC to PPI + MC). An alternative therapy is a 14-day quadruple regimen of a PPI (twice daily) plus bismuth (subsalicylate, 2 tablets 4 times daily) plus metronidazole (250 mg 4 times daily) plus tetracycline (500 mg 4 times daily) (PPI + BMT).[42]

Recommendations

Eradication therapies recommended for patients with uninvestigated dyspepsia who are found to be *H. pylori* positive are as follows:

(a) PPI + AC or MC, or ranitidine bismuth citrate + AC or MC (grade A recommendation, level I evidence[42]).
(b) Alternative first-line therapy (grade A recommendation, level I evidence[42])
(c) PPI + BMT (grade A recommendation, level I evidence[42]).

Management of patients with a negative result of testing for *Helicobacter pylori*

Most clinical trials of drug therapy for dyspepsia have assessed patients with functional dyspepsia. These patients have been investigated (usually by endoscopy) before enrolment, and no organic cause of the dyspepsia symptoms has been detected. It is uncertain whether the evidence from these trials can be extrapolated to the patient who presents in primary care with uninvestigated dyspepsia and subsequently is found to be *H. pylori* negative.

A systematic review evaluating drug treatment of functional (nonulcer) dyspepsia showed that many studies had methodologic weaknesses, including small sample, short duration and use of unvalidated outcome measures.[6] Interpretation of these studies is also hampered by the high placebo response rates, ranging from 13% to 73%, with values typically ranging from about 25% to 55%.

The CanDys Working Group evaluated 4 treatment possibilities for patients who present with uninvestigated dyspepsia and are subsequently found to be *H. pylori* negative: antacids, H_2-RAs, prokinetics and PPIs.

Four randomized placebo-controlled studies evaluated the efficacy of antacids in the treatment of functional dyspepsia, and all 4 failed to demonstrate superiority of antacids over placebo.[202–205]

In a recent meta-analysis that identified 19 eligible studies, the efficacy of H_2-RAs was compared with placebo in patients with functional dyspepsia.[206] The odds ratios for the following outcomes were 2.3 (95% confidence interval [CI] 1.6–3.3) for lessening of epigastric pain, 1.8 (95% CI 1.2–2.8) for complete relief of epigastric pain and 1.5 (95% CI 0.9–2.3) for global assessment of improvement. The results for epigastric pain were statistically significant, whereas the 95% CIs for the global assessment included 1.0, which indicates a nonsignificant result. However, owing to the differences in outcome measures in the studies, data from many eligible studies could not be pooled for the statistical analysis. The cautious interpretation of these findings is that there is a modest benefit from H_2-RAs, but the authors are guarded in their conclusion.

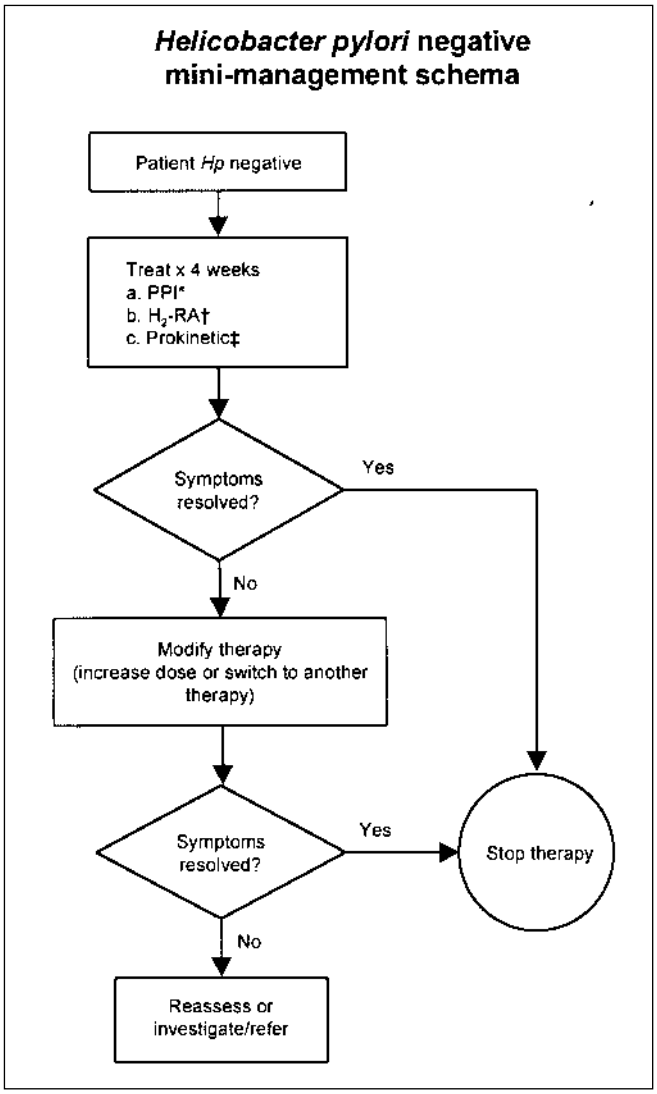

Fig. 5: *Helicobacter pylori*-negative mini-management schema.
***Most of the data available are for omeprazole (20 mg once daily), some for lansoprazole (30 mg once daily).**
†Most of the data are for ranitidine.
‡Data for cisapride only. There are reported adverse cardiac events related to the use of cisapride, and sometimes this can result in serious ventricular arrhythmias and possibly death. This must be taken into consideration before prescribing cisapride.

A meta-analysis of randomized controlled trials assessing cisapride for the treatment of functional dyspepsia included 19 studies.[207] Global assessment of symptoms by the physician or patient was used as the outcome measure in the analysis and was rated on a 4-point scale (no change, or mild, good or excellent response). The odds ratios in favour of cisapride were 2.8 (95% CI 1.5–5.1) for the 12 studies in which the response could be categorized as excellent and 3.3 (95% CI 2.1–5.2) for the 14 studies in which the response could be categorized as good or excellent. These results suggest that there is a modest benefit of cisapride in patients with functional dyspepsia. However, caution is needed in the interpretation because several of the studies had methodologic shortcomings, including small samples.

Most of the trials of PPIs in this area have been conducted with omeprazole. The recent omeprazole studies had large samples and used better-validated outcome measures than earlier trials.[6] Two placebo-controlled trials of functional dyspepsia showed that omeprazole was significantly better than placebo in providing complete resolution of dyspeptic symptoms.[208,209] The larger of the 2 studies involved 1262 patients with functional dyspepsia.[209] After 4 weeks of treatment, complete relief of epigastric pain or discomfort was observed in 38% of the patients who received standard-dose omeprazole (20 mg once daily) (p = 0.002) and 36% of the patients who received low-dose omeprazole (10 mg once daily) (p = 0.02), as compared with 28% of the patients who were treated with placebo. Patients were classified in dyspepsia subgroups according to the most bothersome symptoms. Omeprazole was superior to placebo for complete symptom relief in patients with ulcer-like dyspepsia (40% v. 27%) ($p < 0.05$) and reflux-like dyspepsia (54% v. 23%) ($p < 0.05$) but not in those with dysmotility-like dyspepsia (32% v. 31%).

A randomized placebo-controlled study involving 269 patients with functional dyspepsia treated with lansoprazole (15 mg once daily) showed superior symptom resolution rates after 2 weeks of treatment compared with placebo (62% v. 44%).[210] There was no difference in symptom resolution rates between lansoprazole and placebo in the subgroup of patients who were *H. pylori* negative, but the study did not have enough power to assess this population properly.

Three large randomized trials of omeprazole have been conducted involving patients with dyspepsia in general practice. One trial compared omeprazole (10 mg once daily) with antacid–alginate liquid (10 mL 4 times daily) for 4 weeks.[211] The second trial compared omeprazole (10 mg once daily, increasing to 20 mg and 40 mg once daily as required) with antacid–alginate–ranitidine therapy (10 mL of antacid–alginate 4 times daily, stepping up to 150 mg of ranitidine twice daily and 150 mg of ranitidine 4 times daily as required) in uninvestigated dyspepsia.[212] The final study had 3 treatment arms and compared omeprazole (20 mg once daily) with cimetidine (400 mg twice daily) and placebo in patients with ulcer-like or reflux-like dyspepsia.[213] Omeprazole was found to be significantly superior to every other treatment strategy assessed in these trials. Another study in general practice showed that superior symptom relief was provided by lansoprazole (compared with ranitidine) in patients who presented with ulcer-like and reflux-like dyspeptic symptoms.[214] This study largely included patients with documented GERD or peptic ulcer disease (approximately 70%) and did not provide information about the patients with uninvestigated dyspepsia or analysis according to *H. pylori* status.

Although most studies in this area have used omeprazole, it was the consensus of the CanDys Working Group that other PPIs (lansoprazole[210,214] and pantoprazole [no data]) would likely show comparable efficacy. For this reason, PPIs are listed together for the management schema.

Recommendations

There is good evidence that antacids are ineffective for functional dyspepsia, and they are not recommended for the treatment of uninvestigated dyspepsia in patients subsequently found to be *H. pylori* negative (grade E recommendation, level I evidence[202–205]).

Treatment recommendations for patients who present with uninvestigated dyspepsia and who subsequently have negative results of testing for *H. pylori* are as follows:

(a) PPI (grade B recommendation, level I evidence[208,209]).
(b) H_2-RA (grade B recommendation, level I evidence[206]).
(c) Prokinetic agent (grade B recommendation, level I evidence[207]).

Conclusion

The CanDys Working Group's clinical management tool consists of 5 key steps in the evaluation of patients with uninvestigated dyspepsia. The tool also includes 4 mini-management schemata. The tool is practical, easy to use, explicit and concise, and it reflects the realities of the primary care setting. We believe that adoption of this tool will optimize the treatment of patients with dyspepsia, improve quality of care and be cost-effective.

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Appendix 1: Levels of evidence for rating studies of diagnosis

I	a)	Independent interpretation of test procedure (without knowledge of result of diagnostic standard)
	b)	Independent interpretation of diagnostic standard (without knowledge of result of test procedure)
	c)	Selection of patients or subjects who are suspected of having, but are not known to have, the disorder of interest
	d)	Reproducible description of both the test and the diagnostic standard
	e)	At least 50 patients with and 50 without the disorder
II	Meets 4 of the criteria in I	
III	Meets 3 of the criteria in I	
IV	Meets 2 of the criteria in I	
V	Meets 1 of the criteria in I	
VI	Meets none of the criteria in I	

Appendix 2: Categorization of evidence and recommendations*

Quality of evidence	
I	Evidence obtained from at least one properly randomized controlled trial
II-1	Evidence obtained from well-designed controlled trials without randomization
II-2	Evidence obtained from well-designed cohort or case–control analytic studies, preferably from more than one centre or research group
II-3	Evidence obtained from comparisons between times or places with or without the intervention, or dramatic results in uncontrolled experiments
III	Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees
Classification of recommendations	
A	There is good evidence to support the procedure or treatment
B	There is fair evidence to support the procedure or treatment
C	There is poor evidence to support the procedure or treatment, but recommendations may be made on other grounds
D	There is fair evidence that the procedure or treatment should not be used
E	There is good evidence that the procedure or treatment should not be used

*Adapted from reference 4.

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