Evidence-based recommendations for short- and long-term management of uninvestigated dyspepsia in primary care: An update of the Canadian Dyspepsia Working Group (CanDys) clinical management tool

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The present paper is an update to and extension of the previous systematic review on the primary care management of patients with uninvestigated dyspepsia (UD). The original publication of the clinical management tool focused on the initial four- to eight-week assessment of UD. This update is based on new data from systematic reviews and clinical trials relevant to UD.

There is now direct clinical evidence supporting a test-and-treat approach in patients with nondominant heartburn dyspepsia symptoms, and head-to-head comparisons show that use of a proton pump inhibitor is superior to the use of H_2-receptor antagonists (H_2RAs) in the initial treatment of *Helicobacter pylori*-negative dyspepsia patients. Cisapride is no longer available as a treatment option and evidence for other prokinetic agents is lacking. In patients with long-standing heartburn-dominant (ie, gastroesophageal reflux disease) and nonheartburn-dominant dyspepsia, a once-in-a-lifetime endoscopy is recommended. Endoscopy should also be considered in patients with new-onset dyspepsia that develops after the age of 50 years. Conventional nonsteroidal anti-inflammatory drugs, acetylsalicylic acid and cyclooxygenase-2-selective inhibitors can all cause dyspepsia. If their use cannot be discontinued, cotherapy with either a proton pump inhibitor, misoprostol or high-dose H_2RAs is recommended, although the evidence is based on ulcer data and not dyspepsia data. In patients with nonheartburn-dominant dyspepsia, noninvasive testing for *H pylori* should be performed and treatment given if positive. When starting nonsteroidal anti-inflammatory drugs for a prolonged course, testing and treatment with H_2RAs are advised if patients have a history of previous ulcers or ulcer bleeding.

Key Words: *Acetylsalicylic acid; Aspirin; Dyspepsia; Gastroesophageal reflux disease; NSAIDs; Systematic review*

Recommandations fondées sur des preuves pour la prise en charge à long et à court terme de la dyspepsie non investiguée en médecine de premier recours : Le point sur l'outil de prise en charge clinique du groupe CanDys

Le présent article constitue une mise à jour et une annexe de la revue systématique précédente sur la prise en charge des patients souffrant de dyspepsie non investiguée (DNI) en médecine de premier recours. La diffusion initiale de cet outil de prise en charge clinique insistait sur une évaluation de la DNI échelonnée sur quatre à huit semaines. Cette mise à jour se fonde sur des données récentes issues d'analyses systématiques et d'essais cliniques pertinents.

On dispose désormais de preuves cliniques directes à l'appui de l'approche « tester/traiter » chez les patients qui manifestent des symptômes de dyspepsie non dominés par les brûlures d'estomac, et des comparaisons directes montrent que les inhibiteurs de la pompe à protons donnent de meilleurs résultats que les anti-H_2 dans le traitement initial des patients souffrant de dyspepsie *Helicobacter pylori*-négative. Le cisapride ne fait plus

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partie des options thérapeutiques offertes et les preuves relatives aux autres agents procinétiques sont lacunaires. Chez les patients qui souffrent d'une dyspepsie de longue date, dominée par la présence de brûlures d'estomac (c.-à-d., RGO) ou non, une endoscopie unique est recommandée. L'endoscopie devrait aussi être envisagée chez les patients dont les premiers signes de dyspepsie se manifestent avant l'âge de 50 ans. Les AINS classiques, l'acide acétylsalicylique et les inhibiteurs sélectifs de la COX-2 peuvent tous causer la dyspepsie. S'il est impossible d'en cesser l'usage, on recommande leur coadministration avec un inhibiteur de la pompe à protons, du misoprostol ou un anti-H_2 à forte dose, bien que les preuves reposent sur des données issues d'études sur les ulcères plutôt que sur la dyspepsie. Chez les patients dont la dyspepsie ne se manifeste pas principalement par des brûlures d'estomac, il faut procéder à un dépistage non effractif de *H. pylori* et instaurer le traitement approprié selon les résultats. Lorsqu'on commence un traitement prolongé au moyen d'AINS, il est recommandé de procéder à des tests et de traiter au moyen d'anti-H_2 si les patients ont des antécédents d'ulcères ou d'hémorragies digestives.

The Canadian Dyspepsia Working Group (CanDys) has previously reported the development of an evidence-based clinical management tool (CMT) for patients who present with uninvestigated dyspepsia (UD) to the primary care physician (1). The CMT consists of five steps (Figure 1). For three of the steps, treatment recommendations provide the physician with treatment options listed according to strength of the published evidence, with the most effective treatment listed first.

The CMT uses a definition of dyspepsia that includes heartburn and acid regurgitation symptoms that primary care physicians consider part of the dyspepsia symptom complex (1). This is in contrast to the Rome II Consensus Working Party, which considers heartburn and regurgitation to be diagnostic of gastroesophageal reflux disease (GERD) and distinct from dyspepsia (2). There is more recent support for the CanDys definition of dyspepsia. In two studies (3,4) of *Helicobacter pylori*-positive patients with UD that included the symptom of heartburn, eradication of *H pylori* resulted in improvement of the epigastric pain and in the severity of heartburn. In a large Danish population-based dyspepsia study (5) where patients with reflux symptoms were included, heartburn improved in patients who were successfully treated for their *H pylori* infection. Other data (1,6,7) have confirmed an overlap among dyspepsia and GERD symptoms as defined by Rome II.

The present paper is an extension of the previous work by the CanDys group (1). There are several reasons why an update is necessary. The initial publication of the CMT dealt only with the initial (acute) four- to eight-week management period for UD patients. There is a need for evidence-based recommendations on long-term management. Second, there are new data from primary care-based clinical studies that strengthen the treatment recommendations of the CMT. Finally, certain management questions were not covered in the original CMT, such as once-in-a-lifetime endoscopy in patients with heartburn because of concern about Barrett's esophagus (BE), the role of *H pylori* in GERD, the use of over-the-counter (OTC) medications, and special situations such as the management of dyspepsia in pregnancy.

METHODS

The process for the current update was the same as that used for the generation of the original CMT. CanDys is a multidisciplinary group consisting of academic and community-based family physicians, gastroenterologists and pharmacists. A list of relevant topics was generated and reviewed in detail. For each topic, searches were carried out to identify new clinical trials, systematic reviews (meta-analyses) and/or practice guidelines. All identified articles for each particular topic were retrieved and reviewed by individual members. The subsequent findings were presented to CanDys and extensively discussed, including an assessment of the quality of the evidence. Most searches were initiated broadly (ie, BE and review) and, depending on the question, searches were refined further (ie, risk, adenocarcinoma or treatment). Treatment or management strategy searches focused on identification of new randomized controlled trials, clinical trials or cohort studies. Searches were comprehensive; group members reviewed a large number of citations. Potentially relevant articles were retrieved and checked for further relevant references. Based on these searches and discussions, statements were generated as to which, depending on the topic, was a diagnostic or treatment recommendation, and these were subsequently categorized by the group. Finally, the group voted on all statements. This grading process has been previously described in detail (Table 1) (1,8).

PATIENT REFERRAL MANAGEMENT ISSUES

Evidence for an age cut-off of 50 years to recommend endoscopy

The recommendation for endoscopy in patients over 50 years of age with chronic, stable symptoms stems mainly from expert opinion expressed in practice guidelines. In considering the role of endoscopy, it is important to determine what the findings would be if endoscopy were performed in all patients and whether this would alter management. In the Canadian Adult Dyspepsia Empiric Treatment – Prompt Endoscopy (CADET-PE) study (6), 1040 patients with UD underwent prompt endoscopy within seven to 10 days, without therapy, after presentation to their family physician. The study was designed to provide data on the prevalence of clinically significant endoscopic findings in undifferentiated UD patients. The majority (58%) of UD patients did have clinically significant findings at endoscopy. Esophagitis was by far the most common diagnosis (43%), while duodenal and gastric ulcers were found in 2.8% and 3%, respectively. Esophagitis was more common (55%) in patients with dominant symptoms of heartburn or acid regurgitation. More important, endoscopic esophagitis was seen in 36% of patients who did not have dominant heartburn or acid regurgitation. The majority of patients with gastric (55%) and duodenal ulcers (69%) were *H pylori*-positive. Because symptoms are not good predictors of the endoscopic findings, these data support the significant overlap that exists between dyspepsia and GERD, and argue against the Rome II statement that GERD symptoms define the disease. Finally, the results indicate that endoscopy is unlikely to change medical management and, therefore, it is reasonable to proceed with an empiric trial of therapy as defined in the CMT.

In the CMT, endoscopy is recommended for patients over the age of 50 years who present with new-onset dyspepsia. This recommendation remains unchanged although this age cut-off is largely based on the incidence of gastric and esophageal cancer, which starts to increase significantly over 50 years of age, albeit slowly. Recent data (9-21) confirm that most esophageal and gastric malignancies present with alarm features and, thus, further support that the presence of any alarm

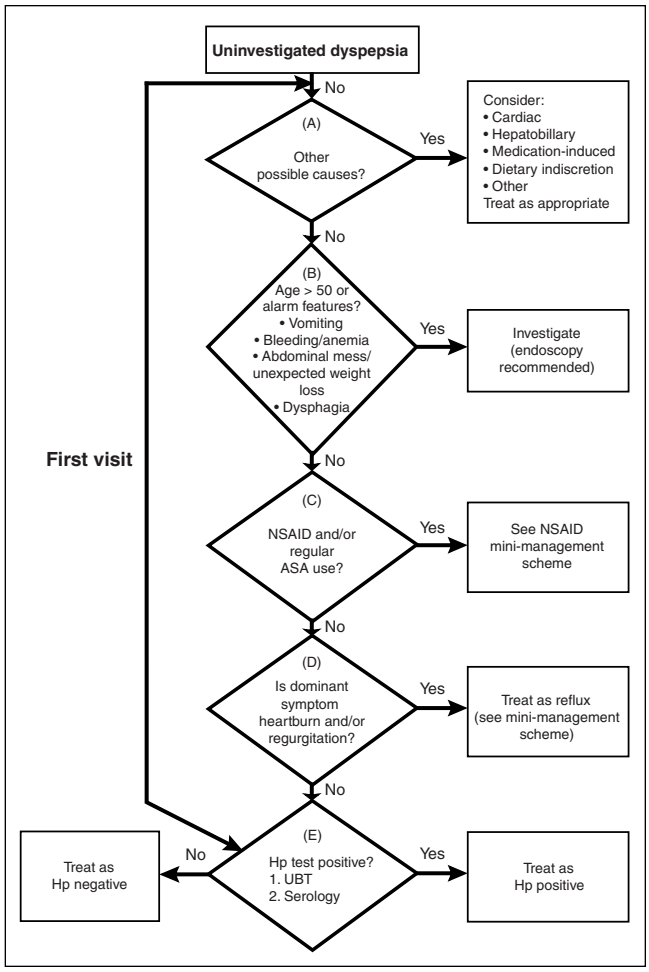

Figure 1) *Clinical management tool, 2000. ASA Acetylsalicylic acid; Hp* Helicobacter pylori; *NSAID Nonsteroidal anti-inflammatory drug; UBT Urea breath test. Adapted from reference 1*

TABLE 1
Categorization of evidence, classification of recommendations and voting schema

Voting on recommendations	
A	Accept completely
B	Accept with some reservation
C	Accept with major reservation
D	Reject with reservation
E	Reject completely
Quality of the evidence	
I	At least one appropriately designed, randomly assigned, controlled trial
II-1	At least one appropriately designed controlled trial without random assignment
II-2	Cohort or case-controlled studies, preferably from one or more research groups
II-3	Substantial or marked results from uncontrolled studies
III	Opinions of experts based on clinical experience or descriptive studies
Classification of the recommendations	
A	Good supportive evidence
B	Fair supportive evidence
C	Poor supportive evidence but recommendations reasonable on other grounds
D	Fair contrary evidence
E	Good contrary evidence

Adapted with permission from references 1,8

feature (vomiting, bleeding/anemia, abdominal mass, unexplained weight loss, dysphagia) is an indication for endoscopy. There are no randomized controlled data to support or refute an age cut-off of 50 years and, therefore, this arbitrary assignment remains based on expert opinion. The American Gastroenterology Association, American College of Gastroenterology, British Society of Gastroenterology and European Society of Primary Care Gastroenterology recommend endoscopy over the age of 45 years (9-12). The 1998 Dyspepsia Working Party report from the World Congresses of Gastroenterology (13) suggests an age cut-off of 50 years in Western nations. The updated British Society of Gastroenterology guidelines (14) suggest an age of 55 years for endoscopy. The recent Scottish guidelines (15) do not suggest an age cut-off due to lack of evidence; however, they do promote that an *H pylori* test-and-treat strategy is appropriate. Undoubtedly, clinical judgement is required (Table 2). In practice, patients with new-onset dyspepsia after 50 years of age compared with those with long-standing symptoms would be considered differently.

Many patients with UD will receive long-term acid suppression. If symptoms persist or recur frequently, it is reasonable to perform endoscopy at least once in the management of the patient's disease to either confirm a suspected diagnosis (eg, esophagitis) or rule out serious underlying disease, especially cancer. Therefore, the authors' suggestion, considering all other factors including age, symptoms, higher-risk populations and physical signs, is that if symptoms have been present (either continuously or frequently recurring) for years, and are without recent change or progression, then endoscopy is likely not required and the short-term CanDys approach may be considered (1). If symptoms are becoming more severe or have recently changed, then endoscopy must be considered.

BE and esophageal cancer

BE is considered a complication of chronic gastroesophageal reflux and is a risk factor for esophageal adenocarcinoma. This should be a consideration when discussing the need for endoscopy, specifically in patients with long-standing heartburn. There is evidence for publication bias, with overrepresentation of studies with relatively small sample sizes reporting higher cancer risks (9,22-44). Although the RR of adenocarcinoma (30- to 100-fold) is increased in patients with BE, the absolute risk remains low (0.4%), as does the risk of dying from the disease (25).

The prevalence of BE (Table 3) does increase with age and is higher in males, especially Caucasians. In the CADET-PE study (6), the overall prevalence of histologically confirmed BE was 2.4% and 4.1% in patients with dominant heartburn or regurgitation, respectively. Because the prevalence of BE is low, it is not necessary to provide early endoscopy for patients with dominant heartburn symptoms. Rather, one might consider endoscopy at a later date (using the presence of reflux symptoms for five to 10 years, severity or ongoing need for acid suppressive therapy as an indication). Because it is difficult to accurately diagnose BE when there is active inflammation in the distal esophagus, it is preferred that endoscopy

TABLE 2
Age cut-off: Incidence and clinical considerations surrounding gastric or esophageal cancer

Risk consideration	Age (years)	Incidence (%) men/women	Clinical consideration
Gastric cancer	<50	0.1/no data available	Chronic stable symptoms for >5 to 10 years
	50 to 60	0.2/0.1	Upper gastrointestinal malignancy unlikely
	60 to 70	0.4/0.3	if alarm features are absent, especially if
	70 to 80	0.7/0.3	<60 years
	80 to 90	0.7/0.4	Is there a good therapeutic response to treatment?
Esophageal cancer	–	No data available	Family history of upper gastrointestinal cancer?

Notes

- Gastric and esophageal cancer rates increase after 50 years of age
- Risk is greater in men than women
- There may be increased risk in subgroups such as immigrants from high prevalence regions
- Test of *Helicobacter pylori* infection due to associated gastric cancer risk

Adapted from references 6,9-15,17-21

TABLE 3
Barrett's esophagus: Relevant data

Definition	A metaplastic change from normal esophageal squamous epithelium to columnar intestinal epithelium. Endoscopically, this is suspected because of a difference in the colour compared with normal esophageal epithelium. The necessary histological hallmark is the detection of intestinal metaplasia in biopsies taken from the lower esophagus. When intestinal metaplasia is accompanied by dysplasia, the risk of malignant transformation is increased
Prevalence:	
Worldwide literature	In all patients undergoing endoscopy, the prevalence is reported between 1% and 3%
	In patients with long-standing heartburn, the prevalence of Barrett's esophagus is 3% to 5% and in some reports as high as 6% to 12%, likely in selected patient groups
Canadian literature	In all patients undergoing endoscopy with heartburn, the prevalence is 0.3% to 2.4%
	In all patients presenting with dyspepsia, the prevalence is 2.4% to 4.1% and 5% in those with dominant heartburn and *Helicobacter pylori*-negative
Treatment	Lifelong proton pump inhibitor, at least standard dose, regardless of the presence of symptoms. Dose titrated up, if required, to achieve adequate symptom control
	Endoscopic surveillance, in accordance with established guidelines

Adapted from references 6,10,17-19,28

be performed while the patient is on maintenance acid suppression therapy for his or her GERD symptoms.

While BE is managed by the specialist, it is important for the primary care physician to understand the issues as they apply to patients presenting with dyspepsia with or without dominant heartburn. In Canada, esophageal cancer is rare (in 2002, 1.4% of the 68,600 new cancer cases in men and 0.6% of the 65,400 new cancer cases in women) and is still less frequent than gastric cancer (27). Over the past two decades, the incidence of all esophageal cancers has not changed. The overall prevalence (five per 100,000) of esophageal cancer (including both squamous and adenocarcinoma) remains low, and did not increase for men and women from 1972 to 1999 (27). However, the incidence of esophageal adenocarcinoma has markedly increased and now represents greater than 50% of all new esophageal cancers. In contrast, the incidence of esophageal squamous carcinoma has decreased. There is an increased risk (OR 7.7) of adenocarcinoma at the gastroesophageal junction in those patients suffering from long-standing reflux symptoms, although the absolute risk, as noted above, is low (28). In contrast, the OR for adenocarcinoma originating in the cardia was 2.2 (28). In that study (28), increased severity, frequency (greater than three times per week), and long duration (greater than 10 to 20 years) of symptoms increased this OR to 16.4 to 20.

Although BE is a risk factor for esophageal adenocarcinoma, most patients presenting with cancer were not known to have BE before their cancer diagnosis (23). Given these data and the evidence for publication bias with over-reporting of the cancer risk, the importance of identifying BE may be overestimated. Nevertheless, there is limited evidence that, with surveillance endoscopy every few years, adenocarcinoma formation in patients with BE is detected earlier and may lead to better outcomes (16,44-47). Recent economic analyses, however, suggest that the yield of surveillance endoscopies is low and may not be cost-effective (48).

The American College of Gastroenterology guidelines (10) on surveillance for patients found to have BE are often followed; ie, endoscopy one to two years after the initial endoscopy and, if no dysplasia is detected after two endoscopies, then endoscopy every third year thereafter. It seems likely in the future that the screening interval may be extended because most patients with dysplasia will be detected early on. More frequent surveillance is required if dysplasia has been detected because of the link between dysplastic changes and malignant transformation but this requires specialist care. It is important that if high-grade dysplasia is found, confirmation of the finding by a skilled gastrointestinal (GI) pathologist is generally recommended. If high-grade dysplasia is confirmed, referral to a centre specialized in treatment of esophageal cancers should be considered.

Treatment of BE aims to optimize acid suppression because there is compelling evidence that BE is a complication of

chronic acid reflux (29). Treatment with a proton pump inhibitor (PPI), usually life long, is recommended as the standard of care for patients with BE (49). Most patients with BE do not complain of dyspepsia symptoms such as heartburn and regurgitation, and this may be due to mucosal insensitivity. However, PPI treatment should be maintained in these patients even if they are asymptomatic. Similarly, if a patient is taking once-a-day PPI and continues to have symptoms, a dose increase can be considered. A PPI rather than an H_2-receptor antagonist (H_2RA) is recommended, given the superior level of acid suppression produced by PPIs. There is very limited evidence that PPI therapy may lead to a decrease in the length of BE or prevent its progression. There is one randomized controlled trial (50) comparing omeprazole with ranitidine over two years which demonstrated that the PPI induced a small but significant partial regression of BE. There is no convincing evidence that antireflux surgery may help prevent the progression of BE to carcinoma. Referral of patients with BE for surgery is not currently the recommended standard of care (51).

Recommendations

1. In patients with long-standing or severe (five to 10 years, more than three times per week), dominant symptoms of heartburn and regurgitation and/or patients requiring long-term maintenance therapy with antisecretory medications (H_2RA, PPI), a once-in-a-lifetime endoscopy is recommended.

Voting on recommendation (level/vote)	A/9 B/2 C/1* D to E/0
Level of evidence	II-2
Classification of recommendation	B

*One vote was cast for accepting with major reservation (C); this individual felt that a once-in-a-lifetime endoscopy could be performed at a later point in time.

2. Once a diagnosis of BE has been made, guidelines for endoscopic surveillance should be followed. Current recommendations suggest a repeat endoscopy every three years if no dysplasia is found after two consecutive annual endoscopies.

Voting on recommendation (level/vote)	A/6 B/6 C to E/0
Level of evidence	II-2
Classification of recommendation	C

3. The management of a patient with BE should include optimal acid suppression therapy, currently achieved with a PPI using the dose that maintains complete symptom resolution.

Voting on recommendation (level/vote)	A/0 B/12 C to E/0
Level of evidence	II-3
Classification of recommendation	C

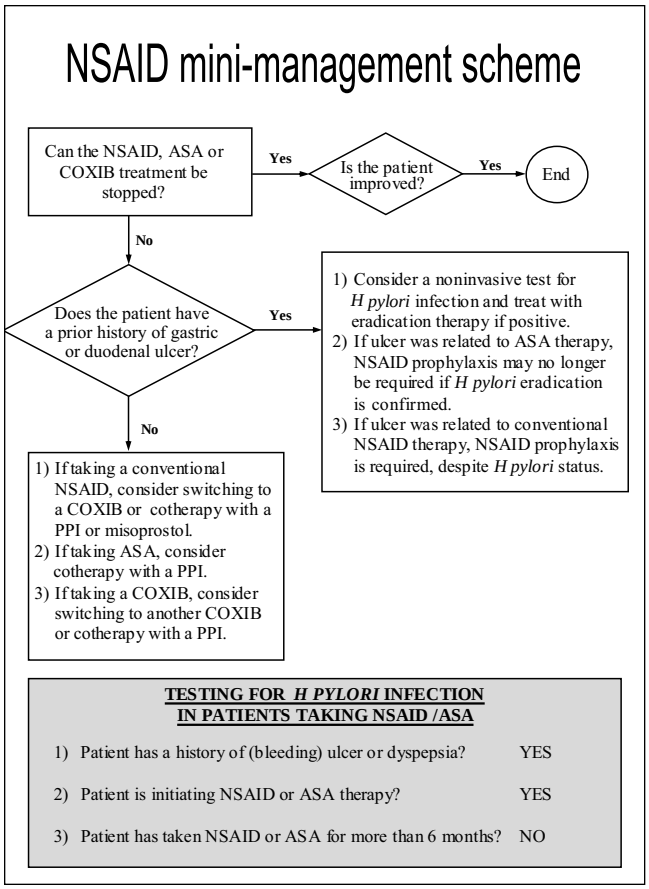

Figure 2) *Nonsteroidal anti-inflammatory drug (NSAID) mini-management scheme. ASA Acetylsalicylic acid; COXIB Cyclooxygenase-2-selective inhibitor; PPI Proton pump inhibitor. Adapted from reference 1*

ACETYLSALICYLIC ACID, CONVENTIONAL NONSTEROIDAL ANTI-INFLAMMATORY DRUGS AND CYCLOOXYGENASE-2-SELECTIVE INHIBITORS

The third step of the CMT deals with acetylsalicylic acid (ASA) or nonsteroidal anti-inflammatory drug (NSAID) use. The recommendations for NSAIDs remain unchanged except regarding areas involving *H pylori* (Figure 2).

NSAIDs, ASA and cyclooxygenase-2-selective inhibitors

Cyclooxygenase (COX)-2-selective inhibitors (COXIBs) have recently come under intense scrutiny because of evidence that their use may be associated with an increased risk of cardiovascular events. This has led to withdrawal from the market of rofecoxib; recent reports also question whether celecoxib and perhaps valdecoxib and naproxen have similar adverse cardiovascular side effects. It seems likely that use of all COXIBs and perhaps some NSAIDs will be re-evaluated in the near future. The following recommendations are suggested for patients currently taking or being considered for COXIB or NSAID therapy.

Conventional NSAIDs are known to increase the incidence of gastric and, to a lesser extent, duodenal ulceration, presumably through inhibition of the COX-1 enzyme along with the desired inhibition of the COX-2 enzyme that is needed for its anti-inflammatory effect. COXIBs selectively inhibit the

COX-2 enzyme but spare the activity of the COX-1 enzyme; as a result, it has been postulated that there is considerably less ulcerogenic potential with the COXIBs (52). The benefit of COXIBs appears to be substantial for ulcers, but is much less for dyspepsia symptoms in comparison with conventional NSAIDs (53,54). Indeed, there continue to be questions regarding the use of COXIBs, NSAIDs and ASA and the development of dyspeptic symptoms. All these agents can cause dyspepsia and/or ulceration; however, no clinical data exist to guide management for scenarios where patients are switched from conventional NSAIDs to a COXIB (55,56). Data on the frequency of NSAID-induced dyspepsia are limited. A meta-analysis (57) found that indomethacin, meclofenamate or piroxicam at any dose, and other NSAIDs at high dose but not at low dose, increased the risk of dyspepsia threefold. However, there is evidence (58) that ASA increases the risk of dyspepsia (OR 1.36) compared with placebo. Of note, GI hemorrhage occurs in 2.47% of those taking ASA (50 mg to 1500 mg) compared with 1.42% of nonusers, representing an OR of 1.68 (59). An OR of 1.59 was reported for those taking doses of ASA below 163 mg/day (59). Unfortunately, there are no studies that provide the incidence rate of dyspepsia when patients initiate ASA therapy. Conventional NSAIDs cause dyspepsia at a rate of 13% to 36%; the wide range is largely the result of varying study definitions of dyspepsia (60). The COXIBs (currently celecoxib, rofecoxib and valdecoxib) can also cause dyspepsia. For celecoxib, the reported cumulative six-month dyspepsia rate was 16.5% compared with 19.5% for traditional NSAIDs (53). For rofecoxib, the cumulative six-month dyspepsia rate was 23.5% compared with 25.5% for traditional NSAIDs (54,61). Valdecoxib, which has recently become available, also can cause dyspepsia (62-65). The data on etoricoxib are at this point too preliminary to draw any conclusions (66). If ongoing anti-inflammatory or antiplatelet therapy is required, a switch to a COXIB can be considered or a trial of a PPI added.

There are no available clinical trial data surrounding improvement of dyspepsia on switching from a conventional NSAID to a COXIB. Essentially, the prevalence of dyspepsia while taking a COXIB is slightly lower compared with a conventional NSAID in some reports (53,54), and is not different according to other reports (61,62,64,65). This recommendation is based solely on expert opinion; there are no published data available to support that such a switch improves dyspepsia. The difficulty with ASA-associated dyspepsia is that it may be difficult to discontinue the ASA therapy if it is being taken because of a well-established cardiac or neurological risk. Clearly the benefits and risks of ASA therapy need to be discussed with the patient and may vary depending on whether one is dealing with primary or secondary prophylaxis for neurological or cardiac disease.

Currently, there is much interest and uncertainty regarding patients taking both an NSAID (or COXIB) and ASA. This issue became evident in the Celecoxib Long-term Arthritis Safety Study (CLASS) (53), a large clinical trial of celecoxib and two conventional NSAIDs, which evaluated serious GI events. In this study, there was evidence that, in patients taking celecoxib, concurrent therapy with ASA abolished the protection against GI complications that was provided by treatment with the COXIB alone. The possible explanation for this is that concurrent use of ASA blocks the COX-1 pathway, thereby negating protection against gastroduodenal injury provided by the COXIB (67). Further studies are required to clarify the possible interactions between ASA and COXIBs. Cotherapy of a COXIB with a PPI or misoprostol may be appropriate but there are no studies that have specifically addressed this.

Interaction between NSAIDs and *H pylori*

There now is evidence for synergy between concurrent conventional NSAID treatment and *H pylori* infection in causing ulcers (68-71). The interaction is stronger for duodenal than gastric ulcers (68). There is evidence from one Hong Kong study (71) that, for selected patients diagnosed with an ulcer (the study was not directly applicable to patients with UD symptoms) who were taking ASA, eradication of *H pylori* was as effective in preventing recurrent ulcers as PPI cotherapy. This is in contrast to results using conventional NSAIDs, which are still associated with recurrent ulcers (19%) when used after cure of *H pylori* infection. However, a second study (71) from Hong Kong did not find the same rate of protection in ASA-associated ulcers although, in that study, most bleeding ulcers occurred in *H pylori*-positive patients not cured of their infection, or patients taking concurrent NSAID therapy. Studies are needed in North America to clarify these intriguing findings. These considerations support the practice of NSAID primary or secondary prophylaxis, with a PPI or misoprostol, for preventing peptic ulcer complications according to a patient stratification scheme based on the presence of risk factors (age over 65 years, previous peptic ulcer bleed, corticosteroid use, concomitant use of anticoagulation therapy, frailty). Patients on both an NSAID and ASA may be at an even greater risk although there are limited data for this specific situation (72). Here it is important to emphasize that most of the above data focus on patients with known ulcer complications. This population differs from the primary care patient population with uninvestigated symptoms, which is inclusive of this subgroup, and is the subject of the current paper. It therefore requires consideration when implementing any management approach because a decrease in ulcer risk is clinically important and many, but not all, ulcer cases are associated with dyspepsia (73-78).

Given the interactions between NSAIDS and *H pylori*, the recommendation in patients who are starting, or have recently (under six months) started, an extended course of continuous therapy with conventional NSAIDs or ASA, is to test for *H pylori* and subsequently confirm eradication. There are no data on ulcer and dyspepsia incidence in *H pylori*-positive patients taking COXIBs. For rofecoxib, data from the Vioxx Gastrointestinal Outcomes Research (VIGOR) study (76) were analyzed according to *H pylori* status and no interaction was found between *H pylori* infection and rofecoxib therapy in causing serious GI events. Ulcers were, however, more common in *H pylori*-positive patients. For celecoxib, no data stratified by *H pylori* status are available. Checking for cure of the infection is important because a decreased risk of ulcer and its complications will not be observed if the infection persists. Testing is strongly recommended if patients have a history of previous ulcers, ulcer bleeding, or are diagnosed with a gastric or duodenal ulcer while on ASA, a conventional NSAID or a COXIB. However, while the risk is decreased by *H pylori* eradication, it is not abolished completely. Although results from the Hong Kong studies need further confirmation, the data suggest that patients taking ASA will not need gastric cytoprotection if they are *H pylori*-negative. In contrast, patients on conventional NSAIDs still

need prophylaxis despite being *H pylori*-negative because the risk of ulcer remains high. There are no data available to guide management in patients taking COXIBs who are *H pylori*-negative after eradication therapy.

Testing is not routinely recommended in long-term (over one year) NSAID or ASA users who have not experienced dyspepsia or ulcers because the risk of ulcer bleeding complications is low in patients who have not had a bleed within their first year of use (68,70). Caution is warranted if an NSAID is prescribed to a patient already taking ASA (or vice versa) because the second medication may increase the ulcer risk (77,78). More data are needed on the interaction between ASA and either conventional NSAIDs or COXIBs to provide clarification in this area.

Recommendations

4. Conventional NSAIDs or COXIBs can be a cause of dyspepsia. Preferably the drug should be discontinued to determine whether the dyspepsia resolves.

Voting on recommendation (level/vote)	A/12 B to E/0
Level of evidence	III
Classification of recommendation	C

5. If stopping the NSAID or COXIB is not possible, consider switching to a different NSAID or COXIB.

Voting on recommendation (level/vote)	A/4 B/8 C to E/0
Level of evidence	II-3
Classification of recommendation	C

6. If the NSAID or COXIB cannot be stopped, cotherapy with a PPI, misoprostol or high-dose H_2RA may be considered, although the evidence is for ulcer prophylaxis and not dyspepsia.

Voting on recommendation (level/vote)	A/9 B/3 C to E/0
Level of evidence	I (NSAID) II-2 (COXIB)
Classification of recommendation	C

7. If the ASA cannot be stopped, cotherapy with a PPI should be considered.

Voting on recommendation (level/vote)	A/2 B/10 C to E/0
Level of evidence	I
Classification of recommendation	B

8. Testing for *H pylori* infection is strongly recommended, and proof of eradication advised, if patients have a history of previous ulcers, ulcer bleeding, or are diagnosed with a gastric or duodenal ulcer while on ASA, a conventional NSAID or a selective COXIB.

Voting on recommendation (level/vote)	A/11 B/1 C to E/0
Level of evidence	II-2 (ASA) II-3 (NSAID) III (COXIB)
Classification of recommendation	C

GERD AND HEARTBURN SYMPTOMS

Initial patient management – further evidence

There are only limited direct data on the comparison of different empirical therapies in uninvestigated patients with reflux symptoms in a primary care environment. A recent meta-analysis (79) of primary care patients with dominant heartburn has shown that the benefit of PPI over H_2RA therapy was larger for nonendoscoped compared with investigated patients. Due to the paucity of data, recommendations for the management of heartburn-dominant UD are made by extrapolation from the combined healing and symptom resolution results of studies in patients with erosive esophagitis or nonerosive reflux disease (NERD, also referred to as endoscopy-negative reflux disease).

There are conclusive data from acute and long-term studies (80-84) that PPIs provide significantly better healing and symptom relief than H_2RAs (or cisapride) for erosive esophagitis. Similarly, standard-dose PPI is also more effective than low-dose PPI (85-87). Therefore, treatment with a PPI is listed as the first choice. Because there is evidence that a greater proportion of patients will respond to acid suppressive therapy after eight weeks compared with four weeks, it is reasonable to re-evaluate patients after four to eight weeks of initial therapy (80,83,86). The decision whether to initiate therapy with a PPI or H_2RA should be made after a careful discussion with the patient. However, if an H_2RA is chosen and the response is inadequate after four to eight weeks, the patient should be switched to a PPI. With respect to heartburn-dominant UD, the superiority of PPIs was documented in a meta-analysis (79) of empirical therapy for GERD, and this analysis also suggested that low-dose PPIs are less effective than standard-dose PPIs for empirical therapy. There are data showing small differences between PPIs with respect to healing, symptom relief and maintenance of remission in patients with erosive esophagitis, but the implications of these findings have yet to be established for symptom management in the larger population of patients with heartburn-dominant UD (87-89).

The recently completed CADET Heartburn-Dominant (CADET-HR) study (83) compared initial therapy with a PPI or H_2RA followed by on-demand treatment with a PPI or H_2RA on relapse of symptoms. The results from this study support that a PPI provides better symptom relief than an H_2RA. After four to eight weeks of treatment, relief of heartburn was 55% for those started on a PPI compared with 27% for those started on an H_2RA. Of patients started with an H_2RA, 47% needed to be stepped up to a PPI due to inadequate symptom relief. Comparatively, 26% of those starting with a standard-dose PPI needed to be stepped up to higher dose PPI treatment.

For patients with erosive esophagitis, symptom relief at four weeks in response to treatment with a PPI was associated with healing of esophagitis in approximately 80% of patients (80). There are Canadian data in uninvestigated

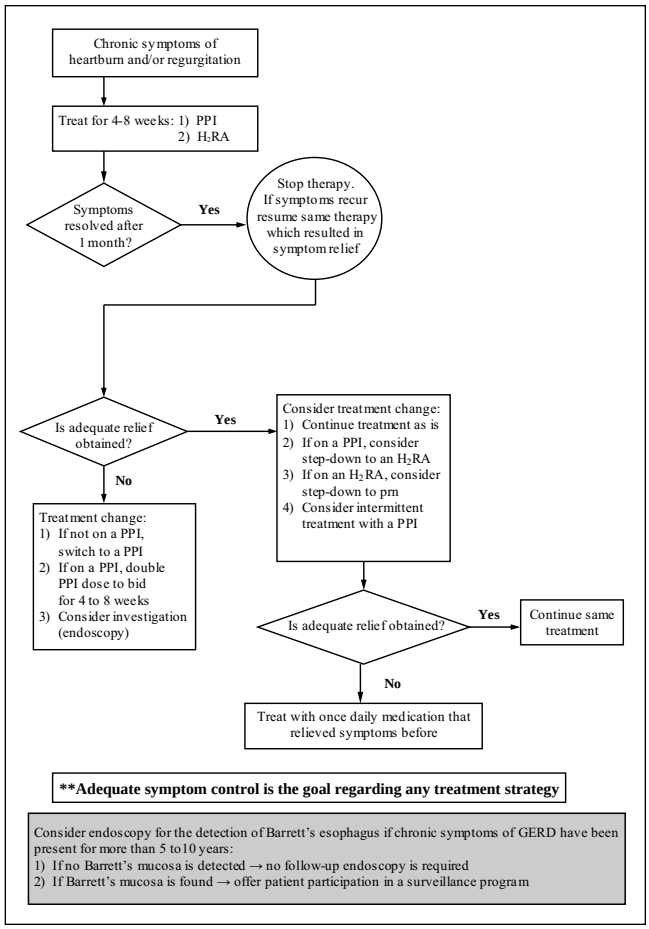

Figure 3) *Reflux mini-management scheme. bid Twice daily; GERD Gastroesophageal reflux disease; H_2RA H_2-receptor antagonist; prn As needed; PPI Proton pump inhibitor. Adapted from reference 1*

patients with heartburn-dominant or -nondominant dyspepsia that show that a longer duration of treatment improves the response rate. Data from the Canadian Confirmatory Acid Suppression Test (CAST) study (90) showed a significant increment in symptom resolution if treatment with esomeprazole 40 mg once a day was extended from one to four and eight weeks in patients with heartburn-dominant UD. Thus, the response to initial therapy with a PPI should be evaluated after four to eight weeks of treatment although, in cases where symptoms continue to be unacceptable after four weeks, the physician may choose to review the patient sooner.

The role of endoscopy in dyspepsia patients with long-standing dominant heartburn

In large cohorts of patients in managed care populations, approximately 2% to 3% have chronic acid-related disorders (91-93). If a patient is unable to discontinue acid suppressive therapy or has been on acid suppressive therapy for five to 10 years, he or she should be considered for referral for endoscopy if this has not been performed previously. Because there is some evidence that patients have a fear of serious underlying disease (eg, cancer), a normal endoscopy can provide important reassurance to the patient and physician (94,95). A discussion between the patient and physician should include the fact that the risk of serious disease is low and this may help in the decision around the request for and timing of an endoscopy. In patients with long-standing heartburn, the main indication for endoscopy is to exclude complications of esophagitis such as stricture, BE or dysplasia (16).

Recommendation

Please refer to "BE and esophageal cancer – Recommendation 1"

The patient with symptoms of heartburn and acid regurgitation for five to 10 years who has a normal endoscopy without evidence of BE requires no further follow-up endoscopy unless symptoms change or alarm features develop (96-99). There are no data to indicate that younger patients with a normal endoscopy should have a repeat endoscopy later in life. This recommendation assumes that patients receive optimal acid suppressive therapy for control of their symptoms, defined as treatment that leads to complete or near complete control of symptoms.

Long-term management options for patients with dominant heartburn

Medical options for long-term therapy in patients with recurrent symptoms include continuous, intermittent or on-demand use of drugs (Figure 3). Long-term therapy with PPIs and H_2RAs has been demonstrated to be effective and safe (100-106). If PPIs are used initially, then consideration may be given to subsequently trying an H_2RA, although data to support such an approach are limited (107,108). There is evidence that a small proportion of patients can tolerate stepping down but, in the majority of patients, the data show that step-down treatment should not be considered because it leads to worsening of symptoms (107,108). Step-down treatment should not be attempted if the patient remains symptomatic on PPI therapy.

Patients with reflux esophagitis or NERD have a reflux symptom relapse rate of over 80% after therapy is stopped. Relapse usually requires medication, either continuously or intermittently, for control. It is reasonable to attempt withdrawal of regular therapy for GERD because a small proportion (less than 20%) of these patients does not need any pharmacological intervention when assessed at six months to one year (107-110). In the CADET-HR study (83), 75% of these patients relapsed within eight to nine days after first becoming symptom-free and stopping their medication. Thus, the majority of patients will require some form of maintenance therapy.

On-demand therapy, for which patients only take medication during periods when they are experiencing symptoms, is attractive because it leads to decreased use of medication and, hence, drug-related costs. However, data are only available for patients with NERD and not UD (111-116). Alternatively, intermittent dosing (a daily two- to four-week course taken when symptoms recur) is a consideration, but this has only been studied in duodenal ulcer patients before the era of *H pylori* infection (110,116).

Antireflux surgery as a long-term management approach is an option for patients who require ongoing medication to control their symptoms or in those who have ongoing symptoms despite medical therapy (37,117). Indications for surgery are changing but a 1999 multivariate analysis (118) concluded that the patients who benefitted the most from an antireflux procedure were those whose symptoms were already controlled on medical therapy. In that study, the best predictors, in order of success, were: 24 h abnormal pH profile, heartburn as the dominant symptom and response to medical therapy. In

Canada in 1996, the rate of antireflux surgical therapy was 11.4 (7.5 abdominal, 0.9 thoracic, 3.0 laparoscopic) per 100,000 population, with a 5.5% average increase in the use of laparoscopic procedures between 1992 and 1996 (119). Few head-to-head comparisons (120-126) of open versus laparoscopic antireflux procedures have been reported. Functional outcomes, up to two years, appear comparable between the two procedures; however, there is no long-term outcome comparison available. Lundell et al (127) reported their five-year follow-up of a randomly assigned clinical study comparing open antireflux surgery with continuous omeprazole therapy. Overall quality of life did not differ between the two groups, but the surgical group had more dysphagia and inability to belch than the medical group. During long-term follow-up (mean 10.6 years), more than 40% of operated patients required acid suppression for symptom control (125). In addition, this study reported that laparoscopic fundoplication has a small (less than 1%) but definite risk of serious complications. CanDys recommends that antireflux surgery only be considered in a small proportion of patients and only after a thorough specialist investigation.

Novel endoscopic techniques have been recently developed that create a barrier to reflux by enhancing lower esophageal sphincter (LES) pressure. These techniques use suturing, injection of a biopolymer or creation of tissue damage using a high radio frequency stimulator at the gastroesophageal junction. There are no head-to-head comparative studies of current treatment alternatives; data (128-130) are short-term with suboptimal selection of outcomes. None of these treatment modalities can currently be recommended in routine practice.

Recommendations

9. Patients with frequently recurring symptoms of dominant heartburn and/or regurgitation should be treated with the same treatment that led to adequate control during initial treatment.

Voting on recommendation (level/vote)	A/11 B/1 C to E/0
Level of evidence	I
Classification of recommendation	A

10. In patients with dominant symptoms of heartburn and/or regurgitation, maintenance therapy with a PPI is more effective for symptom control than with an H_2RA, for both acute and long-term therapy.

Voting on recommendation (level/vote)	A/12 B to E/0
Level of evidence	I
Classification of recommendation	A

11. Antireflux surgery should only be considered for those who are unable or unwilling to take long-term acid suppressive medication.

Voting on recommendation (level/vote)	A/10 B/2 C to E/0
Level of evidence	I
Classification of recommendation	A

Management of patients with long-standing dominant heartburn and *H pylori* infection

In Canada, the overall prevalence of *H pylori* infection is 25% to 30% (6). Age is an important risk factor. Most studies, including CADET-PE (6,131-134), have shown a lower prevalence of *H pylori* infection in patients with esophagitis compared with those without. *H pylori*-infected patients may have gastritis in the body of the stomach which may decrease gastric acid output and thereby lower the potential for acid reflux and resultant esophagitis. There has been controversy over whether cure of *H pylori* infection might provoke or lead to worsening of GERD. Most of the evidence (135-140) shows that this is not the case.

Patients with GERD who require long-term acid suppression, especially with a PPI, and who are infected with *H pylori*, have a worsening of gastritis in the body of the stomach (141). This deterioration of histological gastritis is not seen in *H pylori*-negative patients taking PPIs or in those in whom *H pylori* infection has been cured (142-147). Several randomly assigned controlled trials (148,149), however, have shown that cure of the *H pylori* infection leads to regression of the body gastritis. To date, there is no evidence that the deterioration in gastritis has serious long-term consequences (such as gastric cancer). Hence, it is the CanDys recommendation that a routine 'test for *H pylori* and treat if positive' strategy is not necessary in patients requiring long-term PPI therapy (over one year).

Recommendation

12. Routine testing for *H pylori* is not required for patients on long-term PPI therapy. However, it is reasonable to do so on a case-by-case basis.

Voting on recommendation (level/vote)	A/2 B/6 C/1 D/1 E/0
Level of evidence	II-3
Classification of recommendation	C

Management of patients with nonheartburn-dominant dyspepsia and *H pylori* infection

The CMT recommendation for patients with dyspepsia who are not using NSAIDs or ASA and who do not have dominant symptoms of heartburn is a noninvasive test for *H pylori*, and treatment if the test is positive. The CADET *H pylori* (CADET-Hp) study (3) compared a one-week PPI-based eradication regimen with placebo (empirical twice-a-day PPI) treatment given for one week, to determine whether *H pylori* treatment does lead to long-term improvement in dyspepsia symptoms. This study of 296 patients showed that there was symptomatic improvement at 12 months in 50% of patients, in whom *H pylori* infection was cured, compared with 36% of controls with persistent infection (P=0.02). The number needed to treat to achieve one long-term success was seven patients. It is important to note that while all patients presented with a primary complaint of epigastric pain, a proportion (30%) of the patients also had dominant heartburn and/or regurgitation.

A post hoc subgroup analysis suggested that, in a small population of patients, heartburn symptoms will improve after *H pylori* eradication. The benefit of curing *H pylori* has been supported in other studies as well (150-153). The benefits of the test-and-treat approach are probably derived mainly from treatment of underlying ulcer disease and possibly improving a small proportion of functional dyspepsia patients (150-153). The lifetime risk in an *H pylori*-infected individual to develop ulcers is 5% to 15% (154,155). It is important to note that, despite successful treatment of the infection, a substantial proportion of patients (at least 50%) will require ongoing treatment for dyspepsia symptoms. In such cases, three options exist: retest for *H pylori* infection using a urea breath test (UBT) to ensure the infection has been cured; institute empirical therapy in accordance with the CMT recommendations; or perform endoscopy if clinically indicated, at which time biopsies for *H pylori* infection should be taken.

Recommendation

13. In patients with dyspepsia who do not have alarm symptoms or symptoms of dominant heartburn or acid regurgitation, and are not using NSAIDs or ASA, a test for *H pylori* should be ordered and the patient treated if positive.

Voting on recommendation (level/vote)	A/10 B/2 C to E/0
Level of evidence	I
Classification of recommendation	A

TREATMENT OF *H PYLORI* INFECTION

Treatment, as recommended in the CMT (1), consists of triple therapy with a PPI twice a day, clarithromycin 500 mg twice a day and either amoxicillin 1000 mg twice a day or metronidazole 500 mg twice a day. Recently, it has been recommended that PPI-clarithromycin-amoxicillin be used first-line because that combination is unaffected by resistance to metronidazole. Although there are limited data, the prevalence of metronidazole resistance in Canada is estimated to be approximately 20% (156-160). First-line use with a metronidazole-containing regimen is a reasonable alternative for patients with a penicillin allergy. Regarding the duration of eradication treatment, the recommendation continues to be seven to 10 days for the first treatment (161,162). Recent data (156,163,164) suggest that bismuth-based quadruple therapy may be as effective as PPI-based triple therapy and, therefore, could be considered as an alternative first-line therapy. However, this therapy is more complicated and involves taking 18 tablets a day. All PPIs available in Canada (esomeprazole, lansoprazole, omeprazole, pantoprazole and rabeprazole) have similar efficacy in curing *H pylori* with combinations of clarithromycin-metronidazole or clarithromycin-amoxicillin (165-167). Eradication failure is a concern because PPI-clarithromycin-amoxicillin or PPI-clarithromycin-metronidazole combinations are not successful in 15% to 25% of cases (168). Quadruple therapy (PPI twice a day, bismuth subsalicylate two tablets four times a day, tetracycline 500 mg four times a day and metronidazole 250 mg to 500 mg four times a day) for 10 to 14 days is the preferred therapy for *H pylori* treatment failures (156,164,168).

Recommendations

14. Patients who are *H pylori*-positive should be treated with a combination of PPI, clarithromycin and amoxicillin for seven to 10 days. PPI-clarithromycin-metronidazole can be used if the patient is allergic to penicillin.

Voting on recommendation (level/vote)	A/12 B to E/0
Level of evidence	I
Classification of recommendation	A

15. Quadruple therapy (PPI plus bismuth-metronidazole-tetracycline) for 10 to 14 days is an acceptable first-line alternative.

Voting on recommendation (level/vote)	A/12 B to E/0
Level of evidence	I
Classification of recommendation	A

Diagnostic tests for *H pylori*

The most frequently used diagnostic test for *H pylori* infection is serology. The UBT is recommended because it has a higher positive predictive value (predicting the true presence of infection) and negative predictive value (predicting the true absence of infection) compared with serology, over a broad infection prevalence range (169,170). However, the UBT is not readily available across Canada and access may be limited due to lack of reimbursement. For serology, the negative predictive value is high (over 90%) while the positive predictive value is reduced to 70% to 80%, especially in individuals less than 40 years of age who have a lower (less than 20%) *H pylori* prevalence (170). This means that when serology is used, a significant proportion of patients will be treated based on false-positive test results.

The European *Helicobacter pylori* Study Group has recommended use of the stool antigen test of *H pylori* detection (171). This procedure has not been adequately tested and is not available in the primary care setting (or most secondary or tertiary settings) in Canada and, therefore, is not recommended by CanDys.

Testing for *H pylori* infection following treatment

It is not mandatory to routinely test patients following an eradication attempt unless they have ongoing or recurrent symptoms (171). Testing for cure of *H pylori* should be performed in all patients who have had a bleeding ulcer, and acid suppression therapy should be continued until it is determined that the patient is *H pylori*-negative, with the caveat that they should discontinue PPIs seven to 14 days before a UBT to minimize the risk of a false-negative study. Serology is not an acceptable follow-up test because antibodies may remain detectable for over 12 months despite successful cure of the infection (170). If UBT is not available, endoscopy with biopsies may be performed to document cure if the endoscopy is clinically indicated. Should the patient continue to be *H pylori*-positive, retreatment with an alternative eradication therapy is recommended.

In Canada, the success rate of *H pylori* eradication treatment is high (75% to 85%) and, therefore, it is likely that, once treated, patients will become *H pylori*-negative. Acid suppressive therapy is the treatment of choice for ongoing symptoms, and it is reasonable to start this treatment as soon as the patient

returns for management of symptoms rather than awaiting the results of further *H pylori* testing.

It is recognized that PPIs suppress *H pylori*, although cure of the infection with PPI monotherapy is very rare (172,173). Up to 20% of patients may test falsely negative for the infection if PPIs are used at the time that a UBT is performed (174-180). The recommendation is to stop PPIs for 14 days before the UBT (181,182). In practice, this may be difficult because some patients will have worsening of symptoms during this interval. Often this can be bridged with the use of antacids. For H_2RAs, the recommendation is to stop for seven days before testing because they too can have an effect on *H pylori* (183,184). In practice, it may be reasonable to use two weeks as a guideline for all such medications. Antimicrobials and bismuth compounds must be discontinued for four weeks before a UBT to avoid false-negative test results.

Recommendations

16. Patients who have ongoing or recurrent dyspepsia symptoms following *H pylori* treatment should be tested by UBT (not serology) or undergo endoscopy with biopsies to determine whether *H pylori* is present.

Voting on recommendation (level/vote)	A/11 B/1 C to E/0
Level of evidence	I
Classification of recommendation	A

17. If the patient continues to test positive (not serology) for *H pylori* infection, retreatment with an alternative regimen should be given, for which quadruple therapy is the treatment of choice.

Voting on recommendation (level/vote)	A/11 B/1 C to E/0
Level of evidence	III
Classification of recommendation	C

18. If the patient retests negative, he or she should be treated as an *H pylori*-negative dyspepsia patient with acid suppression as defined in the CMT.

Voting on recommendation (level/vote)	A/3 B/9 C to E/0
Level of evidence	III
Classification of recommendation	C

Management of *H pylori*-negative patients

The CMT recommends treatment for four to eight weeks with a PPI or H_2RA for *H pylori*-negative patients who are not using NSAIDs or ASA, and whose symptoms do not suggest GERD. There is evidence (185-191) that, for this patient group, a PPI provides superior efficacy compared with an H_2RA or a prokinetic agent. As well, a greater proportion of patients will respond after eight weeks of treatment, compared with after four weeks (85).

Few long-term efficacy studies have been published in *H pylori*-negative dyspepsia patients; however, available data indicate that PPIs provide better efficacy compared with H_2RAs. The CADET *H pylori*-negative (CADET-HN) study (188) compared a PPI, an H_2RA, a prokinetic agent and placebo in uninvestigated *H pylori*-negative dyspepsia patients. After four weeks of continuous treatment, those given a PPI had a superior response (51%) relative to that of the other three treatments (36%, 30% and 23%, respectively; P=0.01). This study had a five-month follow-up phase during which patients continued the same drug in an on-demand fashion. Response rates in the on-demand phase, during which patients on average took medication every other day, were not as high as during the acute treatment phase. The proportion of patients who were responders at both four weeks and six months were: omeprazole 31%, ranitidine 21%, cisapride 13% and placebo 14% (P<0.05, omeprazole versus cisapride or placebo).

The CMT was published in June 2000 when the prokinetic agent cisapride was still available. This agent has since been withdrawn from most markets due to rare but possibly life-threatening cardiac arrhythmias. Cisapride is currently available only under special authorization for patients with severe gastroparesis; it should not be used for the treatment of dyspepsia. For the two other available prokinetic agents (domperidone and metoclopramide), there is very limited evidence (190,191) regarding efficacy in dyspepsia. However, in clinical practice, patients who do not respond to high-dose acid suppression therapy are often tried on prokinetic agents despite limited published clinical data to support such an approach.

Recommendations

19. Patients with *H pylori*-negative dyspepsia should be treated with a course (four to eight weeks) of acid suppressive therapy as recommended in the CMT.

Voting on recommendation (level/vote)	A/12 B to E/0
Level of evidence	I
Classification of recommendation	A

20. In patients with *H pylori*-negative dyspepsia, PPIs are more effective than H_2RAs in symptom control, for both acute and long-term therapy.

Voting on recommendation (level/vote)	A/12 B to E/0
Level of evidence	III
Classification of recommendation	C

Management of nonresponders

In the case of a patient (either heartburn-dominant or non-heartburn-dominant *H pylori*-negative) with only partial or no symptom response to a course of standard-dose acid suppression, the CMT recommends to increase the degree of acid suppression to a PPI if an H_2RA was given, increase the dose of a PPI to twice a day, or treat for a further four to eight weeks with the same dose. There are no clinical trial data for the last approach. If a patient fails to improve with a course of double-dose PPI for four to eight weeks, it is unlikely that the symptoms are acid-sensitive, and the PPI should be discontinued, symptoms reviewed and the patient investigated further (eg, endoscopy).

Recommendation

21. If, after a course of initial standard-dose acid suppression, a patient does not respond to a further

four to eight weeks of high-dose PPI, then further investigations, such as endoscopy, may be required.

Voting on recommendation (level/vote)	A/12 B to E/0
Level of evidence	III
Classification of recommendation	C

Management of partial responders

It is uncertain how to manage patients with a partial symptomatic response. There is no set definition for a partial response; however, it can typically be defined by one or more of the following: incomplete symptom control, return clinic visits or unwillingness to continue prescribed therapy. Medication compliance may play a role because there is a theoretical advantage to the administration of PPI once a day (in the case of a single standard dose) given 30 min to 60 min before breakfast, the time when acid pumps are most readily blocked (192-195). It is rational to consider a switch in medication or increase in dose of the treatment for another four- to eight-week period (if on an H_2RA, switch to a PPI and if on a PPI, give a higher split dose), despite lack of supportive data for this approach.

Recommendation

22. If a patient has not responded, or has only partially responded, to a four- to eight-week treatment with an H_2RA or a PPI, consider switching to a PPI if the patient was on an H_2RA, or if on a PPI, doubling the dose of the PPI for another four to eight weeks.

Voting on recommendation (level/vote)	A/11 B/1 C to E/0
Level of evidence	III
Classification of recommendation	C

OTC medications

Several epidemiological studies (196) have shown that a high percentage of people with dyspepsia have tried OTC products as an initial step in management of their symptoms. OTC drugs include antacids, alginate-based products, H_2RAs, bismuth products and herbal products. Published studies of these agents include few randomly assigned controlled trials and relate to a broad spectrum of patient populations, primarily functional dyspepsia or heartburn-predominant dyspepsia patient populations.

Antacid products have been shown to provide symptomatic relief of heartburn in some but not all studies (197), but have no effect on healing of erosive esophagitis. They may provide more prompt symptom relief than OTC doses of H_2RAs (198). Thus, the evidence suggests that antacids should be used for unpredictable episodes of heartburn and for symptomatic 'breakthrough' episodes of heartburn. Several studies (199,200) suggest that the benefit of antacids probably stems from their ability to provide intraesophageal neutralization of acid rather than neutralization of acid present in the stomach. H_2RAs in OTC formulations containing one-half of the prescription strength product per unit dose (eg, ranitidine 75 mg, famotidine 10 mg) do lower gastric acid secretion (201,202). Randomly assigned controlled trials (203-206) of these agents (low-dose OTC cimetidine, ranitidine, famotidine) have shown that these products produce significantly greater relief or prevention of postprandial reflux symptoms than placebo. These drugs are well-tolerated with few side effects reported. The ideal use of the OTC H_2RAs is to administer the dose 1 h to 2 h before episodic and/or predictable occurrences of heartburn, such as before meals (27).

Alginate-based products (Gaviscon, GlaxoSmithKline, USA) are approved for heartburn relief only. Both in vitro and in vivo studies (207) have shown that these agents produce their benefit by forming a 'raft' or foamy physical barrier that may prevent gastroesophageal reflux. Alginate products must be taken approximately one-half hour after meals to produce this effect and subsequent benefit; taking these products before or during meals destroys the ability of the alginate to form an effective raft to reside on the gastric contents. Clinical trials (204) demonstrate that various alginate formulations produce heartburn relief significantly better than placebo; comparisons with antacids have produced varying results of benefit of one over the other.

Many herbal product manufacturers and distributors claim efficacy for their products in dyspepsia; however, there are few well-designed randomly assigned controlled trials (208) that substantiate this, and most of these studies are in patients with functional dyspepsia. Only studies of products containing a combination of peppermint and caraway oils reported benefit over placebo, but the evidence is insufficient to support any recommendations.

In all instances when OTC medications do not provide adequate symptom relief for the patient, or symptoms occur frequently, patients should be advised to consult their family practitioner for further discussion and assessment of dyspepsia symptoms.

Recommendations

23. For infrequent or unpredictable episodes of dyspepsia, OTC medication can provide relief.

Voting on recommendation (level/vote)	A/7 B/5 C to E/0
Level of evidence	I
Classification of recommendation	B

24. If the requirement for OTC medications is frequent and/or symptoms influence daily living, then a physician should be consulted.

Voting on recommendation (level/vote)	A/12 B to E/0
Level of evidence	III
Classification of recommendation	C

Pregnancy and lactation

Dyspepsia in pregnancy is common, with heartburn and acid regurgitation reported by 45% to 80% of pregnant women as the most bothersome GI symptoms, especially in the latter half of the pregnancy (2109-210). The high frequency of reflux symptoms likely occurs as a result of increased abdominal pressure due to the growing gravid uterus and a decrease in LES pressure caused by changes in hormonal status (211,212). There is good evidence (213) that abnormal LES pressure

normalizes soon after delivery. There is obvious concern about the use of medications in pregnancy up to the 14th week during organogenesis when teratogenic risks are greatest and therefore have the most potential to damage the fetus. The Motherisk program (http://www.motherisk.org/) may be consulted, accordingly, for drug-specific or breastfeeding information. Recommendations related to drug use in pregnancy stem from data in animals regarding potential teratogenicity. There are data from randomly assigned and nonrandomly assigned studies and reviews in pregnancy (214-222) but their numbers are small. Antacids should be tried first. An H_2RA may be prescribed if antacids fail to provide adequate relief. Most of the safety data for for H_2RAs is for ranitidine. Should H_2RAs not suffice, a PPI can be considered. For PPIs, most of the data come from small cohort studies in women using omeprazole (214). Other data (223) suggest that there is no evidence of measurable teratogenic risk, increased risk of abortion or risk of low birth weight in humans with the use of H_2RAs (particularly ranitidine) or PPIs (particularly omeprazole) during pregnancy. It must be noted that there are limited data with regard to these recommendations and, as such, very judicious and careful use of such medications is required. Meta-analysis data (214) of the Motherisk program suggest that omeprazole is safe. However, the Food and Drug Administration has assigned omeprazole a category C (human data lacking; animal studies positive; or not performed) based on animal data, suggesting possible toxicity in embryos using high doses of omeprazole. This in contrast to lansoprazole (Food and Drug Administration category B: human data reassuring [animal-positive]; or animal studies show no risk) where animal data did not show toxicity (224).

For breastfeeding, the recommendation is to initially try antacids, followed by an H_2RA and then a PPI. For both H_2RAs and PPIs (data are only available for omeprazole), there is evidence (225) that they are excreted in breastmilk but their levels are low and considered unlikely to be of clinical consequence; PPIs, therefore, probably can be used safely. As with all medications, these drugs should only be used if the symptoms are sufficiently severe to require treatment.

Recommendation

25. In pregnancy, or when breastfeeding, treatments for dyspepsia symptoms should be used in the following order:

    a) Antacids

    b) H_2RAs (most data available for ranitidine) or PPIs (most data available for omeprazole)

Voting on recommendation (level/vote)	A/11 B/1 C to E/0
Level of evidence	II-2
Classification of recommendation	B

Dyspepsia and psychosocial factors

Most evidence correlating psychosocial distress with dyspepsia arises from studies (226,227) of investigated, functional (nonulcer) dyspepsia. Patients consulting for dyspepsia are more likely to have experienced psychosocial stress in the preceding six months (228). Socioeconomic challenges, low expectations, depression and less optimism are predictors of poor outcomes in functional dyspepsia (228). Health-related quality of life, measured at one year, is more closely linked to psychological distress than to the severity of dyspepsia (229). Addressing psychological factors can have an important impact on the long-term outcome of related dyspepsia symptoms (227). Although there are no specific data from UD studies, it is reasonable for the physician to determine psychological stressors when a patient presents.

Antidepressants and psychological interventions

Apart from improving mood, antidepressants have also been used in the treatment of functional GI disorders such as irritable bowel syndrome, noncardiac chest pain and functional (investigated) dyspepsia (230). The limited evidence for UD patients in this area precludes any recommendation. There is emerging evidence on selective serotonin reuptake inhibitor treatment and the apparent risk of peptic ulceration associated with its use; however, the data (231,232) centre on the risk of GI bleeding rather than dyspepsia. There are no treatment data in UD evaluating the effect of psychotherapy or other psychological treatment. It is self-evident that, if mood disturbance presents as a health concern, then it should be discussed with the patient (233).

CONCLUSIONS

The CMT described in the present paper provides evidence-based recommendations for both the acute and long-term management of UD patients. In addition to recommendations for patients taking ASA or NSAIDs and patients with either heartburn-dominant or -nondominant dyspepsia, recommendations are provided on once-in-a-lifetime endoscopy in patients with long-standing dyspepsia, the age cut-off above which initial investigation is recommended, and the need for the treatment of *H pylori* infection in patients receiving long-term acid suppressive therapy. Recent clinical data, including primary care-based studies from Canada, have provided grade A, level 1 evidence for many of the treatment recommendations. Future studies should help to optimize the management of dyspepsia in primary care.

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