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Canadian Consensus Conference on the management of gastroesophageal reflux disease in adults – Update 2004

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BACKGROUND: Gastroesophageal reflux disease (GERD) is the most prevalent acid-related disorder in Canada and is associated with significant impairment of health-related quality of life. Since the last Canadian Consensus Conference in 1996, GERD management has evolved substantially.
OBJECTIVE: To develop up-to-date evidence-based recommendations relevant to the needs of Canadian health care providers for the management of the esophageal manifestations of GERD.
CONSENSUS PROCESS: A multidisciplinary group of 23 voting participants developed recommendation statements using a Delphi approach; after presentation of relevant data at the meeting, the quality of the evidence, strength of recommendation and level of consensus were graded by participants according to accepted principles.
OUTCOMES: GERD applies to individuals who reflux gastric contents into the esophagus causing symptoms sufficient to reduce quality of life, injury or both; endoscopy-negative reflux disease applies to individuals who have GERD and a normal endoscopy. Uninvestigated heartburn-dominant dyspepsia – characterised by heartburn or acid regurgitation – includes erosive esophagitis or endoscopy-negative reflux disease, and may be treated empirically as GERD without further investigation provided there are no alarm features. Lifestyle modifications are ineffective for frequent or severe GERD symptoms; over-the-counter antacids or histamine H_2-receptor antagonists are effective for some patients with mild or infrequent GERD symptoms. Proton pump inhibitors are more effective for healing and symptom relief than histamine H_2-receptor antagonists; their efficacy is proportional to their ability to reduce intragastric acidity. Response to initial therapy – a once-daily proton pump inhibitor unless symptoms are mild and infrequent (fewer than three times per week) – should be assessed at four to eight weeks. Maintenance medical therapy should be at the lowest dose and frequency necessary to maintain symptom relief; antireflux surgery is an alternative for a small proportion of selected patients. Routine testing for *Helicobacter pylori* infection is unnecessary before starting GERD therapy. GERD is associated with Barrett's epithelium and esophageal adenocarcinoma but the risk of malignancy is very low. Endoscopic screening for Barrett's epithelium may be considered in adults with GERD symptoms for more than 10 years; Barrett's epithelium and low-grade dysplasia generally warrant surveillance; endoscopic or surgical management should be considered for confirmed high-grade dysplasia or malignancy.
CONCLUSION: Prospective studies are needed to investigate clinically relevant risk factors for the development of GERD and its complications; GERD progression, on and off therapy; optimal management strategies for typical GERD symptoms in primary care patients; and optimal management strategies for atypical GERD symptoms, Barrett's epithelium and esophageal adenocarcinoma.

Key Words: *Barrett's epithelium; Endoscopy negative reflux disease; Erosive esophagitis; Gastroesophageal reflux disease (GERD); Proton pump inhibitor (PPI)*

La conférence consensuelle canadienne sur la prise en charge du reflux gastroœsophagien pathologique : Mise à jour 2004

HISTORIQUE : Le reflux gastroœsophagien pathologique (RGOP) est le trouble acidobasique le plus prévalent au Canada, et il s'associe a une défaillance marquée de la qualité de vie reliée à la santé. Depuis la dernière conférence consensuelle canadienne de 1996, la prise en charge du RGOP a énormément progressé.
OBJECTIF : Élaborer des recommandations à jour fondées sur des faits probants applicables aux besoins des dispensateurs de soins canadiens pour la prise en charge des manifestations œsophagiennes du RGOP.
PROCESSUS CONSENSUEL : Un groupe multidisciplinaire de 23 participants ayant droit de vote ont élaboré des recommandations au moyen de la méthode Delphi. Après avoir présenté les données pertinentes en réunion, la qualité des données probantes, la solidité des recommandations et le taux de consensus ont été classés par les participants d'après des principes acceptés.
ISSUES : Le RGOP s'applique aux individus dont le contenu du reflux dans l'œsophage provoque assez de symptômes pour réduire la qualité de vie, causer des lésions ou les deux. Le reflux négatif à l'endoscopie

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s'applique aux personnes qui souffrent de RGOP et dont l'endoscopie est normale. Une dyspepsie dominée par des brûlures d'estomac non explorées, caractérisée par des brûlures d'estomac ou une régurgitation acide, inclut l'œsophagite érosive ou le reflux négatif à l'endoscopie et peut être traitée empiriquement comme un RGOP, sans examens plus approfondis, pourvu qu'on n'observe aucune caractéristique alarmante. Les changements au mode de vie ne sont pas efficaces à l'égard de symptômes de RGOP fréquents ou graves. Les antiacides ou les inhibiteurs du récepteur H_2 de l'histamine en vente libre sont efficaces pour certains patients atteints de symptômes de RGOP légers ou peu fréquents. Les inhibiteurs de la pompe à protons sont plus efficaces pour la cicatrisation et le soulagement des symptômes que les inhibiteurs du récepteur H_2 de l'histamine. Leur efficacité est proportionnelle à leur capacité de réduire l'acidité intragastrique. La réponse au traitement initial, constitué d'un inhibiteur de la pompe à proton quotidien à moins que les symptômes soient légers et peu fréquents (moins de trois fois par semaine), devrait être évaluée au bout de quatre à huit semaines. Une médicothérapie d'entretien devrait être maintenue à la dose et à la fréquence les plus faibles nécessaires pour maintenir un soulagement des symptômes. Une opération antireflux représente une solution pour une petite proportion de patients. Il n'est pas nécessaire de procéder au dépistage systématique de l'infection à *Helicobacter pylori* avant d'entreprendre le traitement du RGOP. Le RGOP s'associe à l'épithélium de Barrett et à l'adocarcinome de l'œsophage, mais le risque de malignité est très faible. Le dépistage endoscopique de l'épithélium de Barrett peut être envisagé chez les adultes qui présentent des symptômes de RGOP depuis plus de dix ans. D'ordinaire, l'épithélium de Barrett et la dysplasie bénigne exigent une surveillance. La prise en charge endoscopique ou chirurgicale devrait être envisagée en présence d'une dysplasie ou d'une malignité grave confirmée.

CONCLUSIONS : Des études prospectives s'imposent pour examiner les facteurs de risques pertinents, d'un point de vue clinique, à l'apparition du RGOP et de ses complications, à la progression du RGOP avec ou sans traitement, aux stratégies optimales de prise en charge des symptômes classiques de RGOP chez des patients de première ligne et aux stratégies optimales de prise en charge en présence de symptômes non classiques de RGOP, d'épithélium de Barrett ou d'adénocarcinome œsophagien.

Gastroesophageal reflux disease (GERD) imposes an important burden of illness in Canada. In a population survey, approximately 17% of Canadians reported heartburn in the preceding three months and 13% reported moderate to severe symptoms occurring at least weekly (1). GERD significantly impairs quality of life (2-4), both in patients with erosive esophagitis and in those who have no endoscopic evidence of injury (endoscopy-negative reflux disease [ENRD]) (3,5). Although disease-related mortality is low, health-related quality of life (HRQL) is worse in patients with GERD than in patients with diabetes, hypertension, mild heart failure and arthritis (6).

Since the last Canadian GERD Consensus, held in 1996 (7), numerous studies have provided new evidence relevant to the management of GERD with increasing emphasis on symptom-based management (8,9), supported by greater recognition of the importance of ENRD. The role of investigations has evolved as a result of advances in the endoscopic assessment of erosive esophagitis severity (10-12), and a re-evaluation of the role of ambulatory pH monitoring (13). GERD therapy has also changed; in the realm of medical therapy, proton pump inhibitors (PPIs) have assumed greater importance, both at standard and higher doses, histamine H_2-receptor antagonists (H_2RAs) have become available as over-the-counter medications and the role of prokinetic agents has diminished. Antireflux surgery continues to evolve and new endoscopic therapies are under development. As a result of these advances, there is a need for a comprehensive, up-to-date, evidence-based review of GERD management to guide patients, physicians, payers and regulators, as well as the pharmaceutical and medical equipment industry, in their assessment of different strategies for diagnosis and initial and long-term treatment, including pharmacotherapy, endoscopic therapy and antireflux surgery.

The key areas addressed by the 2004 GERD Consensus Update were the prevalence and burden of GERD in Canada, the diagnosis of GERD (including the role of symptoms and investigations), initial and long-term treatment strategies and the management of GERD sequelae including Barrett's esophagus and esophageal cancer. The consensus dealt only with 'typical' esophageal manifestations of GERD. Noncardiac chest pain (NCCP) and possible extraesophageal manifestations of GERD such as laryngitis, hoarseness, dysphonia, cough, asthma and dental disease were not discussed in detail. Several pediatric gastroenterologists participated in the meeting but specific data in children and adolescents were not reviewed; we refer the reader to the North American Society for Pediatric Gastroenterology and Nutrition Clinical Practice Guidelines (14).

METHODS

Statements to define current understanding or positions relevant to GERD were developed according to generally accepted standards (15,16) using a seven-step approach (Figure 1) to address the 37 pertinent criteria of validity (16-21).

Determination of need for updated guidelines

The need for updated clinical practice guidelines on the management of adult patients with GERD was assessed by an initial review of the existing literature and current recommendations relevant to Canadian practice. This assessment revealed significant changes since the publication of the previous Canadian guidelines in 1997 (7), and a proposal to update those guidelines was, consequently, approved by the executive of the Canadian Association of Gastroenterology (CAG).

Membership of the Consensus group

A steering committee, selected in consultation with CAG, invited experts in the areas of GERD management, evidence-based medicine and continuing medical education to join a multidisciplinary group that comprised 23 voting participants, including Canadian and international gastroenterologists, endoscopists, family physicians and surgeons (Appendix). Nonvoting observers included physicians (members of CAG) and representatives from government (Health Canada), the pharmaceutical industry, and distributors and manufacturers of medical equipment (Appendix).

Determination of clinically relevant issues

The issues were identified by means of two needs assessments conducted in Canadian physicians: 44 primary care physicians from the Canadian Association of Primary Care Gastroenterology (CanGut) completed a paper-based questionnaire, while 86 specialists (81 of approximately 450 Canadian gastroenterologists and five surgeons) were polled using interactive, keypad-based voting in a large group setting. Issues identified by the needs assessments were then reviewed to determine whether they could be resolved with the existing knowledge base, were relevant to current practice, and were consistent with current GERD management strategies (16). Members of the steering committee then identified a number of relevant topics that were circulated electronically for review before the

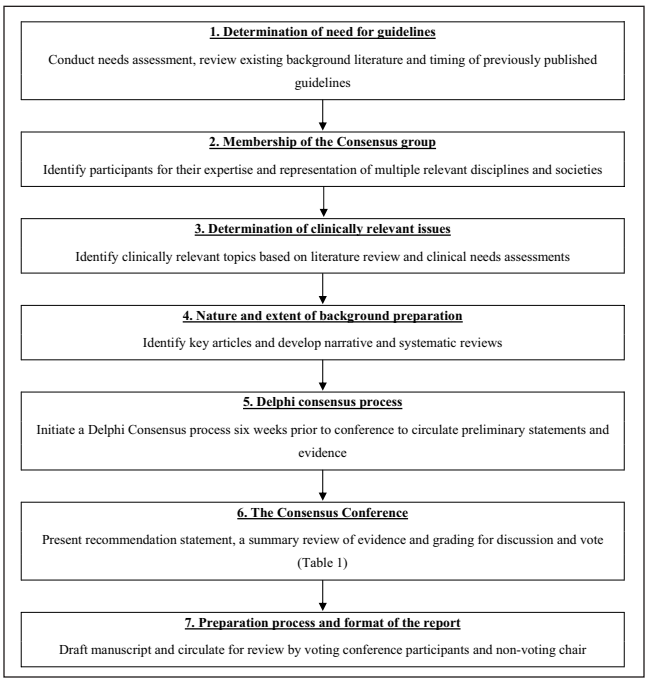

Figure 1) *The adopted process of guideline development. Data from reference 16*

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

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
Voting on the recommendations*	
a	Accept completely
b	Accept with some reservation
c	Accept with major reservation
d	Reject with reservation
e	Reject completely

**Accept statement where more than 50% of participants voted a, b or c*

meeting (22,23); each topic was then used to generate a statement suitable for discussion and revision by the conference participants before undergoing a final vote on its acceptability.

Nature and extent of background preparation

Literature review methods for relevant articles included MEDLINE searches and manual searches of bibliographies of key articles published in English between 1966 and February 2004. Search terms included: "GERD", "erosive and non-erosive reflux esophagitis", "endoscopy-negative reflux disease", "alarm features", "ambulatory esophageal pH monitoring", "Barrett's esophagus", "dysplasia", "healing", "quality of life", "lifestyle modifications", "alginate", "antacid", "histamine-receptor antagonist", "proton pump inhibitor", "endoscopy", "surgical therapy", "economics", "guidelines" and "meta-analysis". Past reviews, meta-analyses and published consensus conferences were used to summarize older data. Narrative reviews were presented at the Consensus Conference before formal voting on the statements that had been identified for discussion at the meeting.

More than 720 articles were reviewed and the Delphi process identified 27 topics for discussion at the meeting. Statements that were identified by the Delphi process as being less controversial or of lower priority were put to a vote without formal discussion during the conference.

Delphi Consensus process

Each statement was graded to indicate the level of evidence available and the strength of the recommendation by using the classification system of the Canadian Task Force on the Periodic Health Examination (Table 1) (24). This classification system was developed to assess literature on therapy rather than literature on prognosis, diagnosis or definitions; the grading procedure was, therefore, modified for some statements, such as those on disease definition and prevalence (24).

General organization

A two-day Consensus Conference was held in March 2004, under the auspices of the CAG according to generally accepted principles (15,16). At the Consensus Conference, data were presented and the statements and the grades attributed to evidence were discussed, modified if necessary, and voted on by each participant according to recognized criteria (Table 1) (9). The CAG secured unrestricted, multipartner funding from the Canadian Institutes of Health Research and industry sponsors, and it administered all aspects of the meeting. Statements of conflicts of interest were obtained from all voting participants (25).

Preparation process and format of the report

A working group drafted the manuscript, which was then reviewed by all voting conference participants and the nonvoting chairs, all of whom approved the final draft. It was then submitted to the Board of the CAG for approval and posted on the CAG Web site for review by the CAG membership before submission for peer review.

STATEMENTS

Each statement is followed by a brief summary, which indicates the quality of supporting evidence, a classification of the recommendation and the results of the participants' vote (Table 1). Statements that only defined terminology were not assigned a level of evidence. Statements marked with an asterisk (*) were put to a vote without formal discussion during the conference (see 'Nature and extent of background preparation').

IMPACT OF GERD

Statement 1: GERD is the most prevalent acid-related disorder in Canada (Level II-1, A; vote: a 86%, b 14%).*

In a population survey of over 1000 Canadians, 17% reported

heartburn in the preceding three months and 13% reported moderate to severe symptoms occurring at least weekly (1). The prevalence of erosive esophagitis in the general population has not been well documented and was thought to be as low as 2% (26,27) although, in one report, endoscopy revealed esophagitis in 8.5% of 355 healthy volunteers (28). The prevalence of erosive esophagitis is probably between one-third to two-thirds among patients with reflux symptoms (29), suggesting a prevalence of 5% to 12% in the general population (5,30-33). In a recent Canadian study (33), which excluded patients whose sole symptoms were heartburn or regurgitation, 37.8% of 1040 primary care patients with previously uninvestigated dyspepsia reported dominant symptoms of heartburn or regurgitation, and of these, 54.7% had erosive esophagitis; overall, 60.5% of the study patients had dominant reflux symptoms or endoscopic esophagitis. Thus, in Canadian patients with uninvestigated dyspepsia (symptoms consistent with an upper gastrointestinal, acid-related disorder), the most common condition was GERD presenting either as typical symptoms or with typical erosive esophagitis, with many others having typical GERD symptoms despite a normal endoscopy (ENRD).

Statement 2: GERD is associated with significant impairment of HRQL (Level I, A; vote: a 90%, b 10%).*

GERD is associated with significant impairment of patients' HRQL (1-4,34) both for patients with erosive esophagitis and those with ENRD (3,5). In general, HRQL is reported to be worse in patients with GERD than in patients with diabetes, hypertension, mild heart failure or arthritis (6).

GERD is also associated with a loss of time from work and with decreased productivity (35,36). A survey of 102 patients with GERD found that 41% reported some lost work productivity because of their disease (35); time off for physician visits and reduced productivity while at work were the most costly losses associated with GERD.

DEFINITIONS

Statement 3: GERD applies to individuals with reflux of gastric contents into the esophagus causing (a) symptoms sufficient to reduce quality of life and/or (b) esophageal injury (vote: a 96%, b 4%).

Statement 4: Heartburn (a retrosternal burning sensation which may rise to the back of the throat) and acid regurgitation are the archetypal symptoms of GERD, which can be treated empirically without further investigation, provided there are no alarm features (Level I, A; vote: a 100%).*

Statement 5: Heartburn-dominant uninvestigated dyspepsia applies to individuals who have symptoms, referable to the esophagus, or a reduced quality of life attributable to gastroesophageal reflux, in the absence of any prior investigations (Level III, A; vote: a 58%, b 37%, c 6%).*

Statement 6: ENRD applies to individuals with GERD who have a normal endoscopy (while off treatment) (vote: a 96%, b 4%).

GERD may manifest with symptoms, esophageal injury or both; if neither is present, the patient with increased acid exposure on esophageal pH monitoring may be considered to have nonpathological gastroesophageal reflux, but not GERD. As indicated above (statement 1), 30% to 70% of patients with GERD symptoms have no esophageal abnormality at endoscopy (5,30-33); this may be because there is no, and never has been, esophageal damage; because previous erosions have healed spontaneously and are not evident at the time of endoscopy; or because the individual is taking, or has recently taken, effective antireflux medication (9,32). Patients in the first category may be considered to have ENRD, while those in the other two categories should be considered to have erosive esophagitis, even if it is not evident at the time of investigation. Unfortunately, it is not clear when pharmacological therapy should be discontinued to ensure that a diagnosis of ENRD is accurate. Although erosive esophagitis recurs rapidly in a high proportion of patients after discontinuation of therapy, 20% to 30% may still be free of erosions for up to six months (37,38). Patients with ENRD are, arguably, the most common subgroup of GERD patients and their symptoms will often respond to effective acid-suppressive therapy (39).

Because most patients with typical GERD symptoms (heartburn and regurgitation) neither undergo, nor require, investigation, one does not know whether they have erosive esophagitis; furthermore, unless they have received effective acid suppression therapy, one does not know whether their symptoms are acid-related and, hence, likely to be attributable to GERD. The term 'heartburn-dominant, uninvestigated dyspepsia' is, therefore, applicable to patients who present with reflux-like symptoms (with or without other dyspeptic symptoms referable to the upper gastrointestinal tract) before they undergo investigation or receive therapy. The Consensus group felt that it was reasonable to diagnose heartburn-dominant uninvestigated dyspepsia as GERD (encompassing both ENRD and erosive esophagitis), and manage it accordingly. The symptom-based approach to diagnosing GERD is a reasonable strategy despite the fact that some patients may prove to have been categorized incorrectly as having GERD on the grounds that antireflux treatment is ineffective (39) or that endoscopy reveals other lesions such as peptic ulceration (33).

The term 'ENRD' used in this document is synonymous with the terms 'nonerosive reflux disease' and 'symptomatic GERD' (40); all three terms are applicable to patients who have typical reflux symptoms and a normal esophagus at endoscopy.

While heartburn and regurgitation are the dominant symptoms of GERD, they frequently coexist with other symptoms such as epigastric pain, epigastric burning and nausea. Other esophageal manifestations of GERD including chest pain and dysphagia, and extraesophageal manifestations including cough, sore throat, hoarseness, shortness of breath and wheezing are less prevalent in GERD patients (41-43) and it is not clear if some of these are 'atypical' GERD symptoms or ancillary symptoms unrelated to GERD.

ASSESSING SEVERITY

Statement 7: GERD symptom severity, incorporating the frequency, intensity and duration of symptoms, is defined by the extent to which the sufferer indicates that it has an adverse effect on his or her daily activities and HRQL (Level II-3, B; vote: a 59%, b 32%, c 9%).*

Statement 8: GERD severity is determined by the severity and frequency of the associated symptoms or by the presence and extent of reflux-related lesions such as esophageal erosions, ulcers,*

hemorrhage, strictures or columnar metaplasia (Barrett's epithelium) (Level I, A; vote: a 76%, b 19%, c 0%, d 0%, e 5%).

Statement 9: In the context of symptomatic management of GERD, 'mild disease' is applicable to patients who have symptoms that are infrequent (fewer than three times/week), of low intensity and short duration, and that have minimal long-term effect on the patient's activities of daily living or HRQL. The terms 'moderate disease' or 'severe disease' are applicable to patients who have more frequent, intense or prolonged symptoms that have a significant effect on the patient's daily activities or HRQL (vote: a 55%, b 45%).*

The severity of GERD should be assessed with respect to the impact of symptoms on an individual's daily activities and HRQL. The effect of GERD on HRQL is dependent primarily on the severity of symptoms, which incorporates frequency, intensity and duration. Impairment of HRQL is very similar for patients with erosive esophagitis and those with ENRD (3,5,31). However, more individuals with severe GERD symptoms report a loss of productivity compared with those with mild symptoms (36). GERD can also be defined by the severity of endoscopic findings (12), because severe erosive esophagitis responds less well to antireflux treatment and relapses more quickly than does mild esophagitis (44-47).

DIAGNOSIS

Statement 10: In clinical practice, a diagnosis of GERD can be made without investigation, based on the presence of the typical symptom of heartburn, with or without regurgitation (Level II-1, A; vote: a 59%, b 27%, c 9%, e 5%).*

Statement 11: A diagnosis of GERD can be made regardless of the frequency or severity of the individual's GERD-related symptoms (Level II-2, A; vote: a 50%, b 27%, c 5%, d 14%, e 5%).*

There is general consensus that patients with dominant symptoms of heartburn or regurgitation can be assigned a clinical diagnosis of GERD and treated without the need for investigations (8,9,48). It has been difficult to document the predictive value of symptoms because there is no accepted gold standard for the diagnosis of GERD, although the use of latent class analysis or Bayesian analysis to integrate the results of three or more independent investigations may, in the future, provide an acceptable gold standard (49). Although patients with heartburn and regurgitation who do not respond to standard antireflux therapy (39) may have functional heartburn rather than GERD (50,51), the majority of the Consensus group felt that heartburn-dominant uninvestigated dyspepsia or ENRD could be treated, initially, as GERD. This approach is supported by data from two surveys of primary care patients with uninvestigated dyspepsia, which indicated that symptoms of epigastric pain, heartburn and regurgitation cluster together, while bloating, belching and nausea form a distinct cluster (33,52). Dominant symptoms of heartburn or acid regurgitation have a high specificity (89% and 95%, respectively) but low sensitivity (38% and 6%) for GERD as defined by abnormal acid exposure on 24 h pH monitoring (53). Using a questionnaire, the presence of heartburn (defined as a "burning feeling in the stomach or lower chest rising up to the neck") had a sensitivity of 73% and a specificity of 43% compared with abnormal 24 h esophageal pH monitoring or erosive disease on endoscopy, and was predictive of symptom resolution during treatment with omeprazole 20 mg (54). However, pH monitoring or endoscopy may be normal in GERD and may, therefore, underestimate the accuracy of symptoms for diagnosis (13). In fact, 24 h pH monitoring is no longer considered to be the gold standard, because it lacks the high sensitivity previously claimed, for the diagnosis of GERD (13). Overall, current 'objective' diagnostic tests for GERD are invasive, costly and insufficiently reliable; furthermore, they are not readily available to most physicians in Canada.

In general, neither symptom severity nor frequency alone constitutes a diagnostic criterion for GERD; for example, reflux-related NCCP is consistent with a diagnosis of GERD even if symptoms are infrequent. On the other hand, mild, infrequent heartburn that does not affect quality of life is not, on its own, considered to be sufficient for a definitive diagnosis of GERD.

It has been suggested that a symptomatic response to PPI therapy can be used for the diagnosis of GERD. A PPI test (one to two weeks of high-dose PPI therapy) has demonstrated a sensitivity of 80%, a specificity of 57%, and positive and negative predictive values comparable with pH monitoring (55-57). However, a PPI test has not been shown to be superior to a trial of standard therapy (58). There was, therefore, consensus that a short-term PPI test was unhelpful before initiating therapy for typical reflux symptoms, because a 'negative' PPI test may deprive many patients of the more prolonged four to eight week course of therapy needed to relieve symptoms (58). A PPI test has high sensitivity and specificity for identifying patients with acid-related NCCP occurring at least three times weekly (59,60), and the one-week test is cost-effective compared with standard investigations (59,61).

INVESTIGATIONS

Alarm features

Statement 12: Alarm features in the presence of GERD symptoms include vomiting, evidence of gastrointestinal tract blood loss, anemia, involuntary weight loss, dysphagia or chest pain (Level III, A; vote: a 68%, b 23%, c 5%, d 5%).*

Statement 13: In patients with GERD, dysphagia should be investigated if it does not completely resolve with adequate PPI therapy (two to four weeks) (Level III, C; vote: a 70%, b 30%).

Statement 14: There is no age threshold (eg, 50 years) that is, by itself, an indication for further investigation for GERD (Level II-2, B; vote: a 91%, b 9%).

Recent guidelines for the management of dyspepsia and GERD have identified alarm features, including persistent vomiting, symptoms or signs of gastrointestinal bleeding, unexplained or involuntary weight loss, dysphagia, choking (acid-induced coughing, shortness of breath or hoarseness) and chest pain, which require prompt investigation (8,9,48,62). This should not be taken to imply that all patients with alarm features require endoscopy; if chest pain is present, cardiac causes should be excluded first and, even for patients with NCCP, investigations other than endoscopy may be appropriate. However, there are few Level I data on which to base these recommendations and there are even fewer data to indicate whether they should always be considered as alarm features. A history of dysphagia, for example, can often be elicited in patients with erosive esophagitis and, if it is mild, it often resolves with acid suppressive therapy (63). On the other hand, if solid food dysphagia is the primary symptom, it should

be considered an alarm feature suggesting peptic stenosis, stricture, esophageal ring or web or esophageal malignancy, and investigation should be expedited, particularly if the dysphagia is progressive or if it does not respond within two to four weeks to adequate PPI therapy.

Although the prevalence of esophageal cancer is higher in individuals over 50 years of age, it is not high enough to justify prompt investigation in all patients who present with GERD symptoms (uninvestigated GERD or heartburn-dominant uninvestigated dyspepsia) for the first time over the age of 50 years (33). Statement 14 is not intended to preclude investigation for Barrett's esophagus in patients over the age of 50 years (see statements 52 to 58), it merely indicates that patients with GERD symptoms should not require investigation solely because they are over the age of 50 years.

Endoscopy

Statement 15: Endoscopy is not required to make a diagnosis of GERD (Level I, A; vote: a 91%, b 9%).*

Statement 16: The role of endoscopy in patients with GERD symptoms is to investigate atypical or alarm features and to detect Barrett's esophagus (Level III, B; vote: a 100%).

Statement 17: The severity of erosive esophagitis is determined endoscopically by the presence and extent of reflux-related 'mucosal breaks' (erosions or ulcers) as defined by the Los Angeles classification (Level I, A; vote: a 82%, b 14%, c 0%, d 0%, e 5%).*

Statement 18: If a patient with GERD symptoms is to undergo endoscopy in clinical practice, it is not generally necessary to discontinue antisecretory therapy before the procedure (Level II-3, B; vote: a 68%, b 18%, c 5%, d 9%).*

Statement 19: Esophageal histology is not required to diagnose GERD in a patient with typical symptoms (Level II-2, B; vote: a 73%, b 27%).*

Up to 70% of patients with symptoms of GERD have no endoscopic evidence of esophagitis and are considered to have ENRD (5,30-33). Thus, although it is highly specific (greater than 90%), endoscopy has lower sensitivity (40% to 60%) (9,64) and is not essential for a diagnosis of GERD. Endoscopy should not, therefore, be considered a prerequisite for any form of pharmacological acid suppression therapy.

Endoscopy is indicated for the majority of patients who present with alarm symptoms referable to the upper gastrointestinal tract (statement 12) (10); under these circumstances, it is useful for the detection of GERD complications such as ulceration, strictures, Barrett's epithelium and esophageal malignancy. The role of endoscopy in the investigation of atypical symptoms is ill defined; it may reveal changes that would support a diagnosis of GERD but a normal endoscopy does not rule out GERD. If endoscopy is performed to identify Barrett's epithelium, the patient should be taking effective antisecretory therapy because it can be difficult to distinguish dysplasia from chronic inflammatory and regenerative changes caused by esophageal injury (65). Erosive esophagitis is best identified by endoscopy, although in clinical practice it is generally unnecessary to differentiate between erosive esophagitis and ENRD. However, in clinical trials in which it is necessary to differentiate erosive esophagitis from ENRD, acid suppression therapy is generally discontinued at least two weeks before endoscopy, recognizing that the time to esophagitis relapse may be much longer in many patients (37,38,46,66). Although there are many endoscopic esophagitis classification schemes, the consensus favoured the Los Angeles system because of its extensive validation for grading the endoscopic severity of erosive esophagitis and its widespread use (Table 2) (10-12,67).

Mucosal biopsies are essential to confirm Barrett's epithelium and to detect dysplasia, but not to diagnose GERD if typical mucosal breaks are present at endoscopy (68). Biopsies or follow-up endoscopies are recommended for deeply ulcerated, extensively eroded circumferential lesions or grossly irregular lesions to distinguish inflammatory ulceration from an ulcerated sessile malignancy. Biopsies are also indicated if a diagnosis other than reflux disease (eg, eosinophilic esophagitis) is suspected. The role of esophageal biopsy for the diagnosis of GERD in ENRD patients with typical symptoms and a normal endoscopy is uncertain. Recent studies (69,70) have confirmed earlier histological findings of basal hyperplasia and papillary elongation in GERD patients (71), and have also shown that these abnormalities, as well as intercellular space dilation, tend to diminish with PPI therapy (72-74), but histology remains unproven as a means of diagnosing GERD. The role of a 'once in a lifetime' endoscopic screening for Barrett's epithelium is discussed under the section on Barrett's epithelium (statements 52 and 53).

Ambulatory pH monitoring

Statement 20: In adult clinical practice, ambulatory esophageal pH monitoring is indicated primarily for the investigation of atypical or persistent symptoms despite appropriate therapy (Level II-1, B; vote: a 77%, b 23%).*

Ambulatory 24 h esophageal pH monitoring has generally been considered the gold standard to detect 'pathological' reflux, with good sensitivity (77% to 100%) and specificity (85% to 100%) in patients with endoscopic esophagitis (13,75). However, it is less reliable for the diagnosis of ENRD with reported sensitivities of 0% to 71%, and specificities of 85% to 100% (13,75) versus symptom-based diagnoses. It may be used to quantify esophageal acid exposure but there is poor correlation between measures of acid exposure (eg, time with esophageal pH below 4.0; DeMeester score) and reflux-related symptoms, esophageal sensitivity or response to acid suppressive therapy. Furthermore, esophageal pH monitoring is impractical in routine practice because it is expensive, cumbersome and not widely available. Esophageal pH monitoring may be appropriate to document abnormal acid exposure in patients with a normal endoscopy who are being considered for surgery; to evaluate patients who are refractory to medical or surgical antireflux therapy; to evaluate patients with atypical GERD symptoms such as NCCP; or to evaluate possible extraesophageal manifestations such as hoarseness, cough or asthma (13). The use of a pH-sensitive telemetry capsule affixed to the esophageal epithelium (Bravo, Medtronic, USA) may improve patient tolerability but experience with this device is limited and, because the capsule is not reusable, it may prove to be too expensive for widespread use in Canada. The role of monitoring bile reflux (bilirubin detector) or nonacid reflux (esophageal impedance monitoring) in the management of GERD remains unclear.

TABLE 2
The Los Angeles classification system for the endoscopic assessment of esophagitis

Grade	Definition
A	One or more mucosal breaks no longer than 5 mm, none of which extends between the tops of the mucosal folds
B	One or more mucosal breaks more than 5 mm long, none of which extends between the tops of two mucosal folds
C	Mucosal breaks that extend between the tops of two or more mucosal folds, but which involve less than 75% of the esophageal circumference
D	Mucosal breaks which involve at least 75% of the esophageal circumference

Data from references 10-12

TABLE 3
Standard once-daily doses of available proton pump inhibitors

Proton pump inhibitor	Daily dose
Esomeprazole (Nexium)*	40 mg
Lansoprazole (Prevacid)†	30 mg
Omeprazole (Losec)*	20 mg
Pantoprazole (Pantoloc)‡	40 mg
Rabeprazole (Pariet)§	20 mg

**AstraZeneca, Canada; †Abbott Laboratories, Canada; ‡Altana Pharma/ Solvay Pharma, Canada; §Janssen-Ortho, Canada. Optimal dosing is 30 min to 60 min before breakfast or supper*

The sensitivity and specificity of barium radiology are insufficiently high for it to be useful for the diagnosis or management of GERD (76).

INITIAL THERAPY

Statement 21: Over-the-counter medications, including alginates, antacids and low-dose H_2RAs, are safe and effective for symptom management in individuals with mild GERD symptoms (Level I, A; vote: a 82%, b 18%).*

Statement 22: Lifestyle modifications, with or without over-the-counter antacids or H_2RAs, are not effective for the management of frequent or severe GERD symptoms (Level II-2, A; vote: a 68%, b 27%, c 5%).*

Over-the-counter medications including alginates, antacids and low-dose H_2RAs are safe and effective for the management of mild and infrequent GERD symptoms (statement 9) in many individuals (9,77), but they have limited efficacy in patients with more severe GERD, including erosive esophagitis, complications or symptoms that reduce HRQL (8,9,78). Although all patients should be educated about factors that may worsen their GERD symptoms, lifestyle modifications alone generally provide inadequate relief for most GERD patients. There are few data on the efficacy of lifestyle modifications in patients with mild GERD, but clinical experience suggests they may be beneficial if there are obvious dietary or pharmacological precipitants, or if obesity, smoking or excessive alcohol use is present.

Statement 23: PPIs are superior to H_2RAs for the reduction of heartburn and healing of esophagitis (Level 1, A; vote: a 100%).

Statement 24: The effectiveness of PPIs and H_2RAs for the healing of esophagitis is proportional to their ability to reduce intragastric acidity (Level 1, A; vote: a 91%, b 9%).

Statement 25: Initial therapy for GERD symptoms should be a once-daily PPI unless symptoms are mild and infrequent (fewer than three times per week) (Level 1, A; vote: a 74%, b 26%).

Throughout the discussions on PPI therapy, standard PPI doses were defined as the daily doses approved in Canada for healing erosive esophagitis: esomeprazole 40 mg, lansoprazole 30 mg, omeprazole 20 mg, pantoprazole 40 mg and rabeprazole 20 mg (Table 3). A meta-analysis of treatment trials, derived from 43 articles in 7635 patients with erosive esophagitis, showed that PPIs heal esophagitis more rapidly and in more patients than do H_2RAs, with overall (two- to 12-week) healing rates of 83.6% (95% CI 79.1% to 88.1%) and 51.9% (95% CI 46.9% to 56.9%), respectively, compared with placebo (28.2%; 95% CI 19.2% to 37.2%) (79). Similarly, a meta-analysis of 13 trials of empirical therapy in 3433 GERD patients and 2520 ENRD patients (39) indicated that PPIs were almost twice as effective as H_2RAs in the empirical treatment of GERD and 20% more effective in the treatment of ENRD (RR 0.55 [95% CI 0.44 to 0.68] and 0.81 [95% CI 0.70 to 0.95], respectively) (39).

GERD severity is related to the degree and duration of esophageal acid exposure (80); the duration of esophageal acid exposure (time during which intraesophageal pH is below 4.0) correlates directly with the degree of mucosal injury (81-84) and severity of symptoms (85). Treatments that prolong gastric acid suppression (time during which gastric pH is over 4.0) are associated with faster symptom relief and higher healing rates (79,86,87). PPIs are significantly more effective than H_2RAs in achieving and sustaining an intragastric pH above 4.0 (80,88); they also produce greater healing and symptom relief than do H_2RAs in patients with confirmed GERD (79,89), and greater symptom relief in patients with ENRD (39) or uninvestigated heartburn-dominant dyspepsia (90). In most studies, PPIs were compared with standard dose H_2RAs but double dose H_2RAs were also less effective than standard dose PPIs (Table 3) for healing erosive esophagitis (91,92), and double dose ranitidine was ineffective in patients who had not previously responded to a six-week course of standard dose ranitidine (93).

In general, 24 h intragastric pH studies suggest that standard dose omeprazole, lansoprazole, pantoprazole and rabeprazole are similar with respect to their effect on the duration of the 24 h period during which gastric pH remains above 4.0 (94-101). However, 24 h intragastric pH studies suggest greater suppression of gastric acidity with esomeprazole 40 mg compared with lansoprazole 30 mg (102,103), omeprazole 20 mg (103,104) and 40 mg (105), pantoprazole 40 mg (103,106) and rabeprazole 20 mg (102,103), although these differences do not necessarily lead to a difference in esophageal acid exposure (107). There also appears to be a dose-response effect for some PPIs (108,109). Corresponding to the pH results, the results of meta-analyses (89,110) suggest that standard dose omeprazole, lansoprazole, pantoprazole and rabeprazole are equivalent to each other with respect to healing esophagitis. While these meta-analyses and the largest available randomized controlled studies suggest that esomeprazole 40 mg produces somewhat higher four- and eight-week healing

rates than standard dose omeprazole (45,47,110), lansoprazole (44) or pantoprazole (111), particularly in more severe (Los Angeles grades C and D) erosive esophagitis, overall differences in healing proportions at eight weeks are small, ranging from just over 3% (44,111) to just over 6% (45,47). Furthermore, although the differences are statistically significant, their clinical relevance is debated and the results have not been replicated consistently in other studies (112).

The proportion of patients reporting symptom relief is somewhat lower for those with ENRD than for those with erosive esophagitis (113); furthermore, higher PPI doses do not appear to elicit a greater response in ENRD (114,115).

The Consensus group made no recommendations with respect to the choice of PPI for initial or long-term therapy, noting that factors such as cost and availability were also important considerations. However, there was agreement that the clear superiority of the PPIs over H_2RAs (with absolute differences in healing rates of 30% to 40%) was sufficient to support the use of PPIs as initial therapy for all patients in whom symptoms have a significant impact on quality of life. In a study comparing step-up and step-down treatment strategies, initial PPI therapy provided faster symptom relief than initial H_2RA therapy, and continued PPI therapy provided better heartburn relief than step-down to an H_2RA, while step-up to a PPI provided better heartburn relief than continued H_2RA therapy (116). Given the excellent safety profile of PPIs and their superior efficacy, there is generally no justification, other than cost or intolerance to PPIs, to use an H_2RA as initial therapy for GERD unless the patient's symptoms are mild or infrequent (see Economics section).

Statement 26: The symptomatic response to an initial course of antisecretory therapy should be assessed at four to eight weeks (Level II-1, B; vote: a 77%, b 23%).*

An adequate course of therapy is at least four to eight weeks. In a study comparing one-week courses of once-daily or twice-daily PPI therapy (PPI test, statements 10, 11) with a four-week standard dose course, the response at one week was highly predictive (positive predictive values 96.1% and 96.3%, respectively) of a good outcome at four weeks, but negative predictive values were low (28.3% and 32.7%, respectively) and almost 15% of patients who did not respond at one week did respond at four weeks (58). Further improvement in response rates was also seen as acid suppression therapy extended from four weeks to eight weeks in patients with erosive esophagitis (healing rates 66% to 81% and 75% to 95%, at four and eight weeks, respectively) (79,89,110,111,117), and the proportion of patients achieving complete resolution of heartburn-dominant uninvestigated dyspepsia increased progressively from four to 16 weeks (90). Clinical assessment of symptoms and quality of life at four to eight weeks is adequate for routine follow-up; endoscopy may be considered but, in general, only for patients with symptoms refractory to PPI therapy or those who develop new or worsening symptoms while on therapy. Failure to respond at eight weeks is not necessarily an indication for specialist referral or endoscopy, because the proportion of responders may increase after this time.

Statement 27: Twice-daily PPI therapy is not generally required as initial therapy for typical GERD symptoms (Level 1, A; vote: a 100%).

Statement 28: Twice-daily, standard dose PPI therapy may be used for patients who have severe symptoms despite standard once-daily PPI therapy (Level II-3, B; vote: a 91%, b 9%).

Statement 29: Twice-daily, standard dose PPI therapy may be used for patients who have severe esophagitis (LA Grade C or D, or stricture) (Level I, B; vote: a 96%, b 4%).

There are few data documenting an increase in healing or symptom relief for double-dose PPI therapy compared with standard dose therapy (Table 3) in patients with typical GERD (118,119); however, reports that, for example, double dose pantoprazole (80 mg) was comparable with single dose pantoprazole (40 mg) have not generally been powered to detect differences of less than 10% between treatment arms (117). Similarly, symptom response rates at one week for patients with uninvestigated dyspepsia, including heartburn-dominant symptoms, were comparable for esomeprazole 40 mg once daily and esomeprazole 40 mg twice daily (58). Half dose PPI therapy (eg, esomeprazole 20 mg, lansoprazole 15 mg, omeprazole 10 mg, pantoprazole 20 mg or rabeprazole 10 mg daily) is less effective than standard dose therapy for acute treatment in erosive esophagitis and ENRD (32,114,120-122) and is not generally recommended for initial therapy.

Conversely, doubling the dose of a PPI reduced esophageal acid exposure in patients in whom single dose therapy was not adequate (100,123). In patients with complicated or atypical GERD, esophageal acid exposure was normalized in all patients with lansoprazole but, of those, 35% required a double daily dose (60 mg) (100). In a similar study, persistently abnormal reflux at esophageal pH monitoring was seen in 29% of patients receiving lansoprazole 30 mg once daily and 68% of those receiving omeprazole 20 mg once daily, but was normalized in all patients after doubling the respective PPI doses (123). Data from pH studies support splitting the double dose and administering it twice daily, before breakfast and supper, rather than once daily (124-126). There is little clinical evidence to support the use of double dose or twice-daily PPI therapy for initial therapy (58). However, several trials have shown that a proportion of patients who had not responded to standard dose PPI therapy experienced symptom relief with double dose PPI or a longer duration of therapy (90,118,127).

Twice daily, standard dose, PPI therapy is used in patients with NCCP or extraesophageal manifestations of GERD but these data were not reviewed formally by the Consensus group.

Statement 30: Prokinetic or promotility agents are not recommended, either alone or in conjunction with antisecretory agents, for the routine initial treatment of GERD (Level II-1, C; vote: a 95%, b 5%).*

A systematic review considered cisapride to be effective for mild-to-moderate GERD in adults (128) but not for GERD in children (129). As empirical therapy for GERD, cisapride was not superior to placebo, and for ENRD, PPIs were superior to cisapride (130). However, concerns about the methodological quality and publication bias have been raised (79,129), and cisapride is no longer generally available. Domperidone produced little or no symptomatic improvement compared with placebo (131-133); in small studies, metoclopramide was more effective than placebo (134) but less effective than ranitidine (135,136).

There are very few data on the efficacy of supplementary prokinetics in conjunction with PPI therapy; the addition of cisapride to standard dose PPI therapy did not result in significant increases in healing rates or symptom relief after either four or eight weeks of treatment (137,138), and the combination of domperidone plus ranitidine showed no benefit over ranitidine alone (139). Omeprazole is twice as effective as the combination of ranitidine plus metoclopramide or ranitidine alone for symptom improvement and healing (140-142), with no significant differences between ranitidine and the combination group (140). In addition, metoclopramide is associated with substantial side effects compared with standard antisecretory therapy, which limits its use (140,142-144).

LONG-TERM THERAPY

Statement 31: 'Continuous' medical maintenance therapy is defined as the daily intake of a medication for an indefinite period to prevent or minimize recurrent reflux-related symptoms or injury to the esophagus (vote: a 91%, b 9%).*

Statement 32: 'Intermittent' medical maintenance therapy is defined as the daily intake of a medication for a predetermined, finite period (usually two to eight weeks) to produce resolution of reflux-related symptoms or healing of esophageal lesions following relapse of the individual's condition (vote: a 86%, b 9%, c 5%).*

Statement 33: 'On-demand' medical therapy is defined as the daily intake of a medication for a period sufficient to achieve resolution of the individual's reflux-related symptoms; following symptom resolution, the medication is discontinued until the individual's symptoms recur, at which point, medication is again taken daily until the symptoms resolve (vote: a 86%, b 14%).*

Although there are no standardized definitions of continuous, intermittent and on-demand (21,145-150) therapy, the above definitions are consistent with those used in many clinical trials and may be appropriate for interpretation of their results, and the development of future clinical studies. It may be argued that intermittent therapy is a 'physician-driven' strategy, whereas on-demand therapy is 'patient driven'. Although clinical experience suggests that many patients take their medication prophylactically to prevent the occurrence of reflux symptoms, this pattern of usage is not included explicitly in the definition of on demand therapy used for clinical studies.

Statement 34: The prime aim of long-term GERD therapy is symptom abolition or control sufficient to normalize the individual's HRQL (Level III, A; vote: a 82%, b 14%, c 5%).*

The primary aim of long-term management of patients with GERD is the control of symptoms and improvement of quality of life (149,151). Because the risk of recurrent endoscopic erosions is extremely high without maintenance therapy (149,152-154), long-term therapy is recommended for erosive esophagitis with the aim of preventing recurrent esophageal injury or mucosal breaks, in addition to complications such as stricture (155-159), hemorrhage, ulceration or Barrett's epithelium. However, the group recognized the lack of evidence that PPI therapy prevents the development or progression of Barrett's epithelium.

Statement 35: An individual whose reflux symptoms have responded well to standard dose PPI therapy may discontinue medication to confirm the need for ongoing therapy (Level II-3, C; vote a 83%, b 17%).

Statement 36: Long-term maintenance therapy should be given at the lowest dose and frequency that is sufficient to achieve optimal control of the patient's symptoms (Level III, B; vote: a 71%, b 10%, c 10%, d 5%, e 5%).*

Statement 37: On-demand acid suppression therapy is a reasonable long-term medical strategy for selected patients with GERD (Level I, B; vote a 55%, b 45%).

Some patients will not require continuous, daily, standard dose therapy for long-term management, but most patients will require some form of maintenance therapy. After discontinuation of therapy, 70% to 100% of patients with esophagitis (37,38,160,161) and approximately 75% of patients with ENRD (31) will relapse within six months.

Half dose PPI therapy is sufficient to maintain endoscopic remission in about 35% to 95% of patients with erosive esophagitis (37,38,46,66,160-163). Similarly, half dose, on-demand PPI therapy produces acceptable symptom control in 83% to 92% of ENRD patients (21,146,148) who have responded previously to acute PPI therapy; however, half dose omeprazole (10 mg daily) is less effective than standard dose omeprazole (20 mg daily) (146), although half dose esomeprazole (20 mg daily) was comparable with standard dose esomeprazole (40 mg daily) (21,146). Although most patients with more severe symptoms or esophagitis require ongoing daily, standard dose therapy to maintain healing and symptom relief (160,164), it was agreed that patients should be maintained on the lowest dose of therapy which was sufficient to provide adequate symptom relief. This presupposes that patients' symptom status will be reviewed to ensure that symptom control is adequate from the patient's standpoint. On-demand therapy may be acceptable because esophagitis recurrence, in the absence of symptoms, occurs in fewer than 9% of patients (160). However, because the majority of studies have been conducted in ENRD patients, there are insufficient data to recommend on-demand maintenance therapy for patients with erosive esophagitis.

There appears to be a dose-response relationship for each of the PPIs (Table 3) in maintenance therapy for erosive esophagitis, presumably related to the degree of acid suppression produced by each treatment regimen. However, the dose-response relationship is less evident for ENRD partly, perhaps, because of difficulty in defining adequate symptom control and partly because there seems to be a ceiling effect such that higher degrees of acid suppression do not appear to be more effective after four weeks of therapy.

Standard dose PPIs are superior to full dose and half dose H_2RAs for maintaining remission of erosive esophagitis (160). Although some studies suggest that, for maintenance therapy, half dose PPIs are equivalent to standard dose PPIs for erosive esophagitis (37,38,66,162,163,165-167) and ENRD (21,148), others indicate higher remission rates with standard dose PPIs than with half or lower dose PPIs both for erosive esophagitis (37,38,160,161,168-170) and ENRD (146). In a large study comparing two half dose therapies, esomeprazole 20 mg daily was superior to lansoprazole 15 mg daily in preventing recurrent esophagitis (46). Although on-demand therapy is effective in ENRD patients, the role of 'alternate day' or 'weekend' therapy in erosive esophagitis is unclear. Omeprazole (20 mg for three days/week or 20 mg on weekends) was inadequate for maintaining endoscopic remission compared with daily omeprazole 20 mg (150,160); lansoprazole 30 mg on alternate

days was less effective than lansoprazole 15 mg daily for maintaining symptom relief although it was equally effective for maintaining healing (167). Overall, half dose PPI therapy is effective for some patients but a proportion will require full dose, or higher-dose maintenance PPI therapy (127,171); this has primarily been documented for erosive esophagitis rather than ENRD. Noncontinuous PPI therapy is effective for ENRD but its role in erosive esophagitis remains uncertain.

Statement 38: Long-term PPI therapy has not been associated with any clinically significant adverse events (Level II-2, A, vote: a 73%, b 27%).*

Long-term PPI use is supported by experience of millions of patient-years of therapy, and a review of omeprazole use for up to 11 years confirmed the safety of PPIs on the gastric mucosa (172,173). Similarly, long-term data from one to five years of use support the safety of esomeprazole (174), lansoprazole (175,176), pantoprazole (162,177,178) and rabeprazole (179). Current evidence suggests that prolonged gastric acid suppression with PPIs rarely, if ever, produces adverse events or clinically significant drug interactions (174,180-182). Diarrhea, abdominal pain, flatulence, headache, eructation, nausea and rash may be reported in a minority of patients (47,174,183-186). The absorption of fats and minerals does not appear to be significantly impaired, and although serum vitamin B_{12} concentrations may be decreased with prolonged use of high dose PPI therapy (eg, Zollinger-Ellison syndrome) (180), there have been no reports of significant clinical sequelae. Concerns over hypergastrinemia, enterochromaffin-like cell hyperplasia and carcinoid formation have not been substantiated during more than 15 years of widespread PPI use in humans (88,152).

Statement 39: Prokinetic or promotility agents are not recommended, either alone or in conjunction with antisecretory agents, for the routine long-term treatment of GERD (Level I, A; vote: a 86%, b 14%).*

Maintenance therapy with cisapride has demonstrated efficacy (137,187) but cisapride is no longer generally available and there are insufficient data to support the use of other prokinetics for maintenance monotherapy. The addition of a prokinetic to PPI maintenance therapy produced no significant added benefit compared with PPI monotherapy (188). There are insufficient published data to make recommendations on the efficacy of other currently available prokinetic agents (128,189-192).

Statement 40: Supplementary nighttime H_2RA therapy is not generally recommended for individuals who have responded incompletely or have failed to respond to standard dose or double dose PPI therapy of adequate duration (Level I, A; vote: a 77%, b 23%).*

'Nocturnal acid breakthrough' has been defined as nighttime periods with gastric pH less than 4.0 lasting for longer than 1 h during twice-daily PPI therapy (193), but there are no data to show that this is clinically significant or that suppression of nocturnal acid breakthrough is beneficial (194,195). Although the addition of an H_2RA at bedtime to PPI treatment can reduce gastric nocturnal acid breakthrough (196-198), there is no evidence that this improves symptoms or quality of life in GERD patients. An evening dose of omeprazole was more effective than a bedtime dose of ranitidine at controlling intragastric pH in healthy volunteers (199); furthermore, tolerance to the nocturnal acid suppressing effects of an H_2RA developed by one week (197).The addition of night time ranitidine in patients with GERD receiving twice-daily omeprazole increased intragastric pH, but there was no significant improvement in reflux events compared with placebo (194).

Statement 41: Surgical antireflux therapy is an alternative to medical therapy for the long-term management of selected patients with GERD (Level I, A; vote a 65%, b 35%).

Although surgery is effective, it shows little long-term advantage over medical therapy and may not eliminate the need for medication in many cases. In a randomized trial, antireflux surgery was superior to PPI therapy in terms of symptomatic relapse, but if patients increased the PPI dose at relapse, there was no significant difference between the treatment strategies at three and five years of follow-up (127,171). Furthermore, in this study, the costs for medical therapy were significantly less than those for surgical therapy at five years (200). In an earlier study (201), antireflux surgery was superior to what was then optimal medical therapy (H_2RA with antacids or metoclopramide, as needed) in improving symptoms and esophagitis for up to two years. However, in a long-term follow-up (median 10 years), 92% of patients in the medical therapy group and 62% of those in the surgery groups were using antireflux medications regularly (202).

Potential indications for antireflux surgery, for patients with typical GERD manifestations, include regurgitation-dominant or volume-related reflux symptoms (although there is no proven superiority for surgery for this indication), dissatisfaction with a need for long-term PPI therapy (whether at stable or increasing doses), poor compliance (for example, due to medication costs) and the presence of a large hiatus hernia. If patients are considering antireflux surgery, they should be aware of its limitations, including the possibility of relapse necessitating repeat surgery or resumption of medical therapy, and the absence of documented benefit in preventing Barrett's epithelium and esophageal adenocarcinoma. Furthermore, it is important to note that factors predictive of a poor outcome following antireflux surgery include a prior lack of response to PPI therapy (203,204). In large case series, the incidence of serious, fatal or life-threatening complications has been less than 1% (205,206). Transient (less than two months) postoperative dysphagia occurs in up to 20% of patients, and longer term dysphagia requiring dilation has been reported in 4% to 9% of patients undergoing antireflux surgery (207,208). The group felt that antireflux surgery is appropriate only at centres where the procedure is performed regularly because the outcome is highly dependent on the experience and skill of the surgeon and support services (209,210). The development of minimal access, laparoscopic techniques has led, in many centres, to increased rates of antireflux surgery but both open and laparoscopic techniques continue to be used. A recent structured review and meta-analysis concluded that laparoscopic fundoplication is as effective as open surgery but with lower morbidity rates and more rapid recovery and discharge from hospital (211).

Statement 42: The role of endoscopic antireflux procedures for the management of GERD in clinical practice has not been adequately defined (Level II-3, D [ie, fair evidence that this procedure should not be used]; vote: a 87%, b 9%, c 4%).

Long-term data on the use of endoscopic techniques and devices are not yet available. Most endoscopic techniques are

intended to increase lower esophageal sphincter pressure or reduce transient lower esophageal sphincter relaxations, thereby decreasing acid reflux. Studies assessing a radiofrequency device (Stretta, Curon Medical, USA), transoral, flexible endoscopic suturing (EndoCinch Suturing System, Bard Endoscopic Technologies, USA), and implantation of polymethylmethacrylate beads (Gatekeeper Reflux Repair System, Medtronic, USA) or a nonabsorbed biocompatible polymer (Enteryx, Boston Scientific, USA) have reported reduced symptoms, medication use and esophageal acid exposure at six to 12 months in some patients with uncomplicated GERD (212-222). However, the improvements in acid exposure were limited, and published trials have only entered patients with mild to moderate GERD; thus, the outcomes of endoscopic therapy cannot be directly compared with those of surgery or standard medical therapy. The Consensus group felt there were currently insufficient published data comparing endoscopic techniques to standard medical or surgical therapy (153) to recommend the routine use of endoscopic antireflux therapy outside the context of a controlled clinical trial.

HELICOBACTER PYLORI INFECTION

Statement 43: Testing for* Helicobacter pylori *infection is not necessary before starting treatment for typical symptoms of GERD (Level I, B; vote: a 82%, b 9%, c 9%).*

Statement 44: The presence of erosive esophagitis at endoscopy does not preclude testing for* H pylori *(Level II-2, A; vote: a 64%, b 32%, c 5%).*

H pylori infection potentiates the acid suppressive effects of PPIs, and patients who are positive for *H pylori* have a higher intragastric pH than those who are negative (223,224). Furthermore, there is some evidence that GERD healing and symptom relief rates with PPI therapy are higher in *H pylori*-positive than in *H pylori*-negative patients (225,226). Because there is no evidence that *H pylori* infection plays a causative role in the pathogenesis of GERD, there is no need for eradication before treating GERD symptoms. This is consistent with published guidelines for the management of uninvestigated dyspepsia, which recommend empiric therapy for typical GERD symptoms before *H pylori* testing is considered (8).

On the other hand, *H pylori* is a class I carcinogen (227) and its eradication improves gastritis in *H pylori*-positive patients with GERD (228). In addition, eradication does not appear to alter the therapeutic dose of omeprazole or cause an increase in reflux symptoms (228). Several studies have also demonstrated that *H pylori* eradication in patients with reflux-like uninvestigated dyspepsia is associated with a reduction in symptoms including heartburn (229-231). In a one-year follow-up study, *H pylori* eradication did not seem to influence relapse rates in patients with GERD (232). Although there is considerable controversy in the literature regarding the effect of *H pylori* eradication on development of GERD (228,232-236), there is no clear consensus that the reported increase in GERD prevalence is causally related to the reduced prevalence of *H pylori* infection in the western world (237,238). Thus, there appears to be no reason why gastric biopsies should not be taken to test for *H pylori* infection if erosive esophagitis is diagnosed at endoscopy.

Statement 45: It is not necessary to test routinely for H pylori *in a patient taking long-term PPI therapy for GERD symptoms (Level II-3, C; vote: a 74%, b 26%).*

Statement 46: Eradication of H pylori *has no clinically relevant, adverse effect on the long-term outcome of GERD (Level I, A; vote a 87%, b 13%).*

Overall, it appears doubtful that *H pylori* infection has any effect on the pathogenic mechanisms determining either reflux or its complications (239). Omeprazole therapy in patients who are *H pylori*-positive led to an increase in corpus gastritis, which was reversed by eradication of *H pylori* (228,240); however, in a later study, acid suppressive therapy for three years did not increase gastric glandular atrophy or intestinal metaplasia in *H pylori*-infected GERD patients (241). *H pylori* infection causes gastritis, regardless of whether there is concomitant acid suppression therapy; although atrophic gastritis is a risk factor for the development of intestinal metaplasia and gastric cancer, there is no evidence to suggest that PPI therapy is an additional risk factor or that *H pylori* eradication affects the risk of gastric cancer in the presence of PPI therapy. Thus, it was not considered necessary to routinely test for *H pylori* in GERD patients receiving chronic PPI therapy; however, in accordance with the recommendations of the Canadian *H pylori* Study Group, patients with a documented *H pylori* infection should be offered eradication therapy (242) and there is no reason to deny eradication therapy to patients requiring long-term GERD therapy.

BARRETT'S EPITHELIUM

Definitions

Statement 47: The presence and extent of reflux-related columnar metaplasia in the distal esophagus should be recorded in a standardized manner as 'endoscopic suspicion of Barrett's epithelium'; a formal diagnosis of 'Barrett's epithelium' requires histological confirmation (Level III, B; vote: a 64%, b 36%).*

Statement 48: Barrett's epithelium is defined as the presence of abnormal epithelium ('endoscopic suspicion of Barrett's epithelium'), of any extent, extending proximally beyond the limit of the gastroesophageal junction, that demonstrates specialized intestinal metaplasia ('esophageal columnar epithelium; intestinal metaplasia positive') on histological examination of the endoscopic biopsies (vote: a 68%, b 27%, d 5%).*

This definition of Barrett's epithelium is comparable with that used in many clinical studies; however, there is no general agreement on a formal definition. The American College of Gastroenterology defined Barrett's esophagus as "a change in the esophageal epithelium of any length that can be recognized at endoscopy and is confirmed to have intestinal metaplasia by biopsy of the tubular esophagus and excludes intestinal metaplasia of the cardia" (243). A change extending less than 3 cm is referred to as short segment Barrett's esophagus while 3 cm or greater is referred to as long segment Barrett's esophagus. The gastroesophageal junction refers to the most proximal extent of the gastric mucosal folds when the stomach is deflated and the esophagus is minimally distended. The true prevalence of Barrett's epithelium is not known, in part because of differences in the diagnostic criteria for Barrett's esophagus. Population-based studies have reported a prevalence of 23/100,000 to 376/100,000 individuals (244,245) but,

among symptomatic patients with GERD, the rate of Barrett's epithelium is higher, at an estimated 2% to 18% (29,246,247). Among patients in whom Barrett's epithelium was found during endoscopy for GERD symptoms, short segment Barrett's epithelium (6% to 10%) was more common than classical Barrett's epithelium (5%) (247). In Canadian, predominantly white patients with uninvestigated dyspepsia, Barrett's esophagus was confirmed in 2.4% of patients overall, including 4.1% in the group with dominant symptoms of heartburn and 1.4% in the remaining patients (33).

Risk of esophageal cancer

Statement 49: Barrett's epithelium is associated with the development of esophageal adenocarcinoma (Level II-3, B; vote: a 96%, b 4%).

It is postulated that gastroesophageal reflux leads to metaplasia such that the normal esophageal squamous epithelium changes to a specialized intestinal glandular epithelium in a small proportion of GERD patients, and that this may then progress, by way of dysplasia (low and high grade) to esophageal adenocarcinoma (248,249).

Older studies suggested that the annual risk of adenocarcinoma in Barrett's esophagus was 1% to 2%, but a recent analysis suggested that this is an overestimate due to publication bias of smaller studies showing higher risks (250). More recent studies suggest that the risk of adenocarcinoma is approximately 0.4% per person-year of follow-up in patients with Barrett's epithelium (202,251-255) compared with only 0.07% per year in patients who do not have Barrett's epithelium (202).

Statement 50: The risk of esophageal adenocarcinoma increases with the severity, frequency and duration of GERD symptoms (Level II-2, A; vote: a 95%, b 0%, c 0%, d 5%).

Patients with a long duration of GERD, especially white males with more severe and frequent reflux symptoms, have a higher risk of esophageal adenocarcinoma (256-261). For example, compared with subjects who had no symptoms, the odds ratios for developing esophageal adenocarcinoma were 7.7 in patients with recurrent reflux symptoms and 43.5 in those with long-standing (greater than 20 years), frequent, severe symptoms (256).

Risk factors for the development of adenocarcinoma in patients with Barrett's epithelium include: white, male, longer duration, severity and frequency of GERD, size of hiatal hernia, obesity, smoking, diet low in fresh fruit, dysplasia (247) and, possibly, the length of esophagus involved by Barrett's epithelium (247). However, many patients with esophageal adenocarcinoma have no identifiable risk factors and no prior diagnosis or symptoms of GERD.

Statement 51: Neither medical nor surgical therapy has been proven to prevent the development or progression of Barrett's epithelium or the subsequent development of esophageal adenocarcinoma (Level I, D [ie, fair evidence that these strategies should not be used for prevention]; vote: a 82%, b 9%, c 5%, d 5%).*

The goals of therapy in patients with Barrett's epithelium include symptom control, maintenance of mucosal healing, regression of Barrett's epithelium, and regression of dysplasia. Management includes acid suppressive medication, ablative therapies or surgery. Four randomized controlled trials have assessed acid suppressive therapy with a PPI, H_2RA or antireflux surgery in patients with Barrett's epithelium (202,262-264). Acid suppression was associated with symptom control but not with disappearance of Barrett's epithelium despite some reports of regression. Antireflux surgery did not prevent progression, with dysplasia developing in 10.5% and adenocarcinoma in 2.5% of 161 patients seven to 21 years postoperatively (265). In two long-term studies, there was no difference in the rate of development of esophageal adenocarcinoma between patients receiving medical or surgical antireflux therapy (202,264). No study has demonstrated a reduction in esophageal adenocarcinoma rates with medical or surgical acid suppression (266). The theoretical potential for benefit from surgery with respect to prevention of malignancy may be outweighed by the operative risks (267), while there are no documented risks to long-term medical therapy with a PPI. For the role of endoscopic ablative therapies in treating established Barrett's epithelium, see statement 61.

Screening

Statement 52: Endoscopic screening for Barrett's esophagus in patients with longstanding GERD has not been shown to reduce mortality from esophageal adenocarcinoma (Level III, C; vote: a 39%, b 44%, c 9%, d 4%, e 4%).

Statement 53: Endoscopy to detect Barrett's esophagus with dysplasia may be considered in adults with GERD symptoms for more than 10 years (Level III, C; vote: a 96%, b 4%).

Although screening for Barrett's epithelium is controversial, guidelines from the American College of Gastroenterology recommend a 'once in a lifetime' gastroscopy for the detection of Barrett's epithelium in patients with chronic GERD symptoms (243). In a recent survey, this strategy was favoured by 76% of Canadian gastroenterologists (268), although it should be noted that this is associated with a high cost and unproven benefit. The rationale for screening patients with chronic GERD is that a long duration of GERD, especially in white males with more severe and frequent GERD, confers an increased risk of Barrett's epithelium and adenocarcinoma (256,257). Other risk factors, including nocturnal reflux symptoms, GERD complications (esophagitis, ulceration, bleeding) and hiatus hernia might also influence the need for screening (247). However, it was estimated that the risk of esophageal adenocarcinoma (0.00065/patient/year) would be lower than the risk of endoscopic complications, based on American population data (77 million adults over 50 years old in the USA, of whom 14% or 10 million had weekly GERD symptoms) (269). In addition, because 40% of patients with esophageal adenocarcinoma do not have weekly reflux symptoms, they would not be identified by a symptom-based surveillance strategy. Although there was support for endoscopy in patients with GERD symptoms for more than 10 years, it was also noted that esophageal adenocarcinoma is very uncommon in patients younger than 50 years of age and therefore, the benefit of a screening endoscopy in such patients remains unproven.

Although many patients with Barrett's epithelium are asymptomatic, general population screening was not recommended. However, patients undergoing endoscopy for any reason should be examined for Barrett's epithelium with confirmatory biopsies if there is endoscopic suspicion of Barrett's epithelium.

The group noted that any screening or surveillance program for Barrett's epithelium would have important implications for health care delivery because of the high cost (CDN$300 for

endoscopy alone [270] to CDN$530 for endoscopy and biopsies [271]) and limited availability of endoscopy in Canada, and the potentially high costs of the programs themselves (272,273). Furthermore, there is no indication for screening and surveillance in patients who are ineligible, a priori, for esophagectomy or ablative therapy because of age or significant comorbidities.

Surveillance

Statement 54: Endoscopic surveillance in patients with Barrett's epithelium should include a standard biopsy protocol and should be performed while the patient continues to take therapy sufficient to optimize symptom relief (Level III, C; vote: a 64%, b 14%, c 18%, d 5%).*

Statement 55: Patients with Barrett's epithelium and dysplasia should generally undergo surveillance (Level III, C; vote: a 83%, b 17%).

Statement 56: In the presence of low-grade dysplasia, surveillance endoscopy should be repeated within 12 months with a concentrated biopsy protocol and repeated annually until there is no dysplasia (Level II-3, B; vote: a 65%, b 35%).

Statement 57: Patients with Barrett's epithelium in the absence of dysplasia should generally undergo surveillance (Level III, C; vote: a 13%, b 48%, c 4%, d 35%).

Statement 58: For patients with Barrett's epithelium, in the absence of dysplasia, enrolled in a surveillance program, endoscopy should be repeated every two to five years (Level III, C; vote: a 4%, b 65%, c 4%, d 26%).

Surveillance is recommended in patients with Barrett's epithelium and dysplasia, because dysplasia (graded as absent, indefinite, low- or high-grade) is a risk factor for esophageal adenocarcinoma. The risk of progression to cancer is greater with high-grade than with low-grade dysplasia (274). Unfortunately, there is significant interobserver variability in the grading of dysplasia, with less than 50% agreement in the classification of low-grade dysplasia (274). The risk of progression from low to high-grade dysplasia or cancer ranges from 10% to 28% over five years (274), and estimates of progression from high-grade dysplasia to cancer range from 16% to 59% over five to seven years (249,275,276). Endoscopy should be performed while the patient continues to take effective antisecretory therapy to minimize the impact of inflammation and regeneration on the interpretation of biopsy specimens (65).

Surveillance in patients with Barrett's epithelium without dysplasia is more controversial. Barrett's epithelium is the only endoscopically identifiable precursor to esophageal adenocarcinoma, a cancer that is increasing in prevalence in Western societies and has a very poor prognosis if not detected early. There is limited evidence that surveillance programs may lead to earlier cancer detection and improved survival (277-279), and retrospective analyses suggest that patients undergoing surveillance had better two-year (86% versus 43%) (280) and five-year (62% versus 20%) (279) survival rates for esophageal cancer than those who did not undergo surveillance.

However, there are also strong arguments against surveillance. There is a low absolute incidence of esophageal cancer in Canada of 4.06/100,000 (281), and the benefits of surveillance are not clearly defined as they are in colon cancer. Surveillance endoscopy is expensive and time-consuming. About 93% to 98% of esophageal adenocarcinomata occur in patients without a prior diagnosis of Barrett's epithelium (247,282). Analysis of patients with esophageal adenocarcinoma in Denmark over a 20-year period found that Barrett's esophagus was diagnosed more than one year before the cancer diagnosis in only 1.3% of cases (282). Finally, it has been suggested that surveillance may be of marginal benefit because most patients with Barrett's epithelium do not die from esophageal cancer (283). During a nine-year follow-up of 166 patients with Barrett's epithelium, only eight patients developed esophageal cancer, which was the cause of death in only two cases (283).

Recommendations for the frequency of surveillance are based largely on cost-effectiveness modelling studies. Using an estimated cancer rate of 0.4% per year, Provenzale et al (251) estimated the costs of surveillance every one to five years compared with no surveillance, with esophagectomy performed if high-grade dysplasia was diagnosed. Based on incremental cost-utility ratios, surveillance every five years was the only economically viable strategy in the USA. More frequent surveillance cost more and yielded a lower life expectancy, due to the need for more endoscopies and a greater incidence of complications. The incremental cost-utility ratio for surveillance every five years was $98,000/quality-adjusted life year (QALY) gained, which, although less than the estimated cost of $590,000 for surveillance every two years, is substantially more than the $20,000/QALY to $22,000/QALY estimated for colon and breast cancer screening. However, because these ratios may not be relevant to a Canadian practice setting, there is a need for modelling studies using Canadian data.

Surveillance, like screening endoscopy (statements 52 and 53), has significant implications for health care resource utilization. Opinion on the advisability of surveillance was divided (statement 57) because of concerns that it was associated with limited documented benefit in the face of significant costs. On the other hand, there was also concern that failure to undertake surveillance would fall below the standard of care implied by the American College of Gastroenterology guidelines (243). Finally, surveillance was not endorsed for patients who are ineligible for esophagectomy or ablative therapy.

Management

Statement 59: When high-grade dysplasia is detected for the first time, endoscopy should be repeated within three months with a concentrated biopsy protocol and expert pathologist review of all biopsies (Level II-3, B; vote: a 83%, b 17%).

Statement 60: In the presence of confirmed high-grade dysplasia or malignancy, expert consultations should be obtained to ascertain the optimal endoscopic or surgical management strategy (Level III, B; vote: a 87%, b 13%).

In most cases, the presence of high-grade dysplasia should be confirmed by repeat endoscopy and biopsies within three months of initial detection after the patient has had continuous treatment with double dose (twice-daily standard dose) PPI to heal associated erosive esophagitis and minimise reflux-related injury, inflammation and proliferative changes. However, for some patients, such as those with multifocal high-grade dysplasia, referral for therapy does not require a repeat confirmatory endoscopy (243).

Endoscopic mucosal resection and ablation are available in some centres for the management of localized, high-grade dysplasia but experience to date is limited (275,284-290). In general, surgery is the recommended strategy for patients who are otherwise healthy but it should be done in centres where these procedures are performed regularly (291). Esophagectomy can be associated with important side effects including dumping syndrome, dysphagia, diarrhea, early satiety and weight loss, and can reduce quality of life substantially (264,292-295). Vagal-sparing esophagectomy and other techniques are under investigation and may be promising in the future. Endoscopic treatments require further study before they can be routinely recommended. Optimal management will generally require input from one or more appropriate specialists in the fields of gastroenterology, oncology, gastrointestinal histopathology and thoracic surgery.

Statement 61: Ablation therapy should be considered for individuals with high-grade dysplasia or esophageal adenocarcinoma who are unfit for or unwilling to undergo surgery (Level I, A; vote: a 77%, b 18%, c 5%).*

Patients with coexisting major medical conditions who are not suitable for surgery may benefit from other therapeutic interventions, including photodynamic therapy (PDT), endoscopic mucosal resection, thermal destruction, Nd:YAG (neodymium: yttrium aluminum garnet) laser ablation, injection therapy, esophageal dilation, placement of prosthetic tubes (296), argon plasma coagulation and bipolar electrocoagulation (297). Two randomized controlled trials have assessed ablative PDT in patients with Barrett's epithelium (284,286,287). Ablation of high-grade dysplasia was accomplished in 80% of patients treated with PDT plus omeprazole compared with 40% of those treated with omeprazole alone (284,285). At two years of follow-up, there were significantly fewer cases of cancer with PDT compared with omeprazole alone (13% versus 28%) (287). However, there is a significant risk of stricture after PDT (37% of patients) and the procedure is costly (284,285). The procedure is most promising for patients not suitable for surgery who have high-grade dysplasia or superficial adenocarcinoma. Several case series have reported positive results with endoscopic mucosal resection (288-290).

ECONOMICS

Burden of illness studies show that GERD is a costly illness, with the highest annual direct costs of all gastrointestinal and liver diseases, at $9.3 billion a year in the USA (298). At $5.89 billion, drugs constituted the largest component of direct costs. In Canada, over $670 million is spent on PPI and H_2RA therapy annually (299).

PPI therapy is a cost-effective alternative to H_2RA therapy for the long-term medical management of GERD (300-305). The higher acquisition costs for PPIs versus H_2RAs are partially offset by gains in health status (304). Treatment with PPIs resolves symptoms more rapidly and prevents symptomatic recurrence more effectively (300,304). Results of decision analysis comparing different empirical treatment strategies with H_2RAs and PPIs demonstrated that initial treatment with PPIs followed by on-demand therapy was a cost-effective approach (301). This strategy produced more QALYs at a lower cost than the H_2RA, step-up, step-down and continuous PPI strategies. The cost-effectiveness ratios were $20,934/QALY gained for patients with moderate to severe GERD symptoms, and $37,923 for patients with mild GERD symptoms versus a reference strategy of lifestyle modification. A Canadian analysis found that PPI maintenance (incremental $98,000/QALY) and intermittent PPI (incremental $12,000/QALY) therapy were more expensive but provided a greater number of symptom-free weeks (7.1 and 5.5, respectively) compared with intermittent H_2RA therapy (reference strategy) (306).

On-demand therapy with a PPI is a cost-effective management strategy both for patients with ENRD (301,307) and for those with mild-to-moderate GERD, including Los Angeles grades A and B esophagitis (308). A pooled analysis of data from three six-month trials (307) found that 90% of patients with ENRD could control symptoms effectively with on-demand esomeprazole 20 mg with 16% to 61% lower direct medical costs compared with either intermittent (four-week acute treatment) or continuous omeprazole treatment.

Medical antireflux therapy may be more cost-effective than surgical antireflux therapy over a five-year time frame (200), although this remains controversial (270). In a randomized controlled trial, 298 patients received either continuing treatment with omeprazole or underwent open antireflux surgery (200). At five years of follow-up, the direct medical costs per patient were lower with medical treatment, but the differences between the two strategies decreased over time. As well, the results were highly dependent on the costs of surgery, which varied greatly among countries (200). However, a Canadian modelling study of medical versus surgical costs found that laparoscopic antireflux surgery was a cost-effective alternative for patients with erosive esophagitis compared with long-term PPI maintenance therapy provided that the symptomatic failure rate was less than 10% per year and that maintenance PPI therapy cost more than $38.60 per month (270). While the initial cost of surgery is higher, it becomes the more cost-effective option at 3.3 years of follow-up. The clinical implications of analyses such as these in clinical practice are unclear in part because the outcomes are dependent on the baseline assumptions – especially the country – on which the modelling is based, and the costs of surgical and medical therapy. The effectiveness and cost-effectiveness of antireflux surgery for other reasons, including extraesophageal GERD and ENRD, has not been studied.

FUTURE DIRECTIONS

Although GERD is one of the most common conditions in the Western world, there is a surprising paucity of information on its natural history, sequelae and the effect of long-term management strategies on outcomes. Future research should focus on areas where data are lacking, to provide evidence that will improve the diagnosis, treatment and, potentially, prevention of GERD and its complications. International consensus on the definition and diagnosis of GERD should be a priority. In addition, more data are needed on:

- risk factors for the development of GERD including diet, obesity, medication, *H pylori* status, genetics and acid secretory status;
- the role of endoscopy in GERD management;
- the long-term prognosis of GERD, on and off treatment;
- the risk of developing Barrett's epithelium and esophageal adenocarcinoma across the spectrum of patients with GERD;

- the relationship between gastroesophageal reflux and the development of NCCP and extraesophageal disease including asthma, chronic cough, wheezing, hoarseness, ear pain, laryngopharyngitis and dental erosions;
- the outcomes and costs for various evidence-based strategies for the management of GERD in clinical practice.

APPENDIX: LIST OF ATTENDEES

Nonvoting chairs: John Marshall (JKM), David Armstrong (DA)

Voting participants: Canadian: Mehran Anvari (MA), Bill Bartle (BB), Naoki Chiba (NC), André Duranceau (AD), Robert Enns (RE), Carlo Fallone (CF), Nigel Flook (NF), Krishnasamy Govender (KG), Roger Hollingworth (RH), Richard H. Hunt (RHH), Liisa Jaakkimainen (LJ), Walter Kutcher (WK), Norman Marcon (NM), Serge Mayrand (SM), Anthony Otley (AO), William Paterson (WP), Joseph Romagnuolo (JR), Dan Sadowski (DS), Phil Sherman (PS), Sander van Zanten (SVZ). International: Ronnie Fass (RF), Peter Kahrilas (PK), Paul Moayyedi (PM).

Represented societies: Canadian Association of Gastroenterology (CAG), CAG Practice Affairs Committee, CAG Endoscopy Committee, Canadian Association of General Surgeons, Canadian Association of Primary Care Gastroenterology (CanGut), College of Family Physicians of Canada, CAG Liason Committee, CAG Pediatrics Committee.

Nonvoting observers: Hassen M Abdullah (Therapeutic Products Directorate, Health Canada), Paul Sinclair (CAG), and representatives of the pharmaceutical industry. The meeting was open for observation by nonparticipating physicians.

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Receipt of consultation fees: Abbott (NC, CF, PS), Allergan (PK), Altana (DA, NC, RE, CF, RF, NF), AstraZeneca (DA, BB, NC, RE, CF, RF, NF, RHH, PK, WP, JR, SVZ), Axcan (RHH), Canadian Medical Protective Association (AD), Enteromedics (MA), Eisai Japan (RF), Eisai USA (RF), GlaxoSmithKline (NF, RHH), Janssen-Ortho (DA, BB, NC, CF, RF, PK, JR, SVZ), Medtronics (PK), Merck Frosst (RHH), Negma (RHH), Nicox (RHH), Novartis (BB, NF, PK, SVZ), Ontario Ministry of Health and Long-term Care (JKM), Pfizer (NF), Solvay (NF), TAP Pharmaceuticals (RF, RHH), Wyeth (RF), Xillix Vancouver (NM).

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Participation in speaker's bureau: Abbott (DA, NC, CF, NF, JKM, SM, WP, PS); Allergan (PK); Altana (DA, NC, RE, CF, NF, JKM, SM, WP, JR); AstraZeneca (DA, BB, NC, RE, CF, RF, NF, RHH, PK, SM, NM, PM, WP, JR); Axcan (NC, NM, JR); Boston Scientific (JR); GlaxoSmithKline (NF); Janssen-Ortho (BB, CF, RF, PK, JR); Medtronics (PK); Merck Frosst (RHH, JKM); Negma (RHH); Novartis (BB, CF, RF, NF, RHH, PK, JKM, SVZ); Pfizer (NC, NF); Solvay (NF, JR); Takeda (PM); TAP Pharmaceuticals (RHH); Wyeth (RF, PM).

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