

Clinical Practice Guidelines on the Diagnosis and Treatment of Gastroesophageal Reflux Disease (GERD)

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Foreword

In the last two decades gastroesophageal reflux disease (GERD), initially thought to be a disease only common in the West, is described increasingly in Asia, including the Philippines. A recent local report indicated that the prevalence of erosive esophagitis (EE), a common complication of GERD, has more than doubled, i.e., 2.9% to 6.3%, between the two time periods of 1994–1997 and 2000–2003, respectively. GERD causes recurrent annoying symptoms which are common reasons for clinic visits and consultations thus, it is the objective of these guidelines to provide both primary care physicians (PCPs) and specialists a current, evidence-based, country-specific recommendations for the optimal management of GERD. These guidelines are intended to empower PCPs to make a clinic-based diagnosis

of GERD, to start an empiric acid-suppressive therapy in the appropriate patient, and direct them to select which GERD patient may need to undergo investigations to ascertain further the diagnosis of GERD or to assess outcomes of therapy. We acknowledge that studies published in the future may influence the impact on our confidence on the recommendations enumerated in these guidelines thus, we commit to update this document when it is deemed appropriate.

Keywords: Gastroesophageal reflux disease, erosive esophagitis, non-erosive reflux disease, refractory GERD, extraesophageal GERD, Barrett's esophagus, proton pump inhibitor, upper endoscopy, heartburn, acid regurgitation, alarm features

Introduction

Background: Gastroesophageal reflux disease (GERD) is an increasingly common disorder that gastroenterologists and general physicians encounter in daily practice. In Eastern Asia, the prevalence of GERD has risen from 2.5–4.8% before 2005 to 5.2–8.5% from 2005 to 2010.¹ The prevalence rate of erosive reflux disease (ERD) reported from our region is between 3.4%–16.3%, figures which are almost similar to those reported in the West.^{2–8} In Asia, time trend studies during the last two decades reveal that the prevalence of erosive esophagitis (EE) has increased from 1.8% in 1995 to 12.6% in 2002.^{9–13} In the Philippines, the prevalence of EE increased from

2.9% to 6.3% between two time periods, 1994–1997 and 2000–2003, respectively.¹³ On the other hand, it is estimated that 11–12% of the general population have non-erosive reflux disease (NERD) and a considerably higher proportion of symptomatic patients presenting for endoscopy may suffer from NERD, i.e., 37–87%.¹⁴

The bothersome symptoms of GERD and its associated morbidities result in loss of productivity and a diminished quality of life.^{15,16} In addition, concerns that long-term symptomatic GERD may be a risk factor for adenocarcinoma of the distal esophagus has put the disease high in the consciousness of and a source of anxiety for both physicians and patients.¹⁷ These are common reasons for clinic visits and consultations thus, it is our objective to provide the primary care physicians (PCPs), as well as, the specialists an updated, evidence-based, country-specific set of recommendations for the current management of GERD.

Methods: In order to assess the needs of local medical practitioners regarding the proper diagnosis and treatment of GERD a core working party composed of ten (10) members (JDS, LIG, MADL, SQdO, AAP, RNG, CDD, RPR, AJGG and JCB) was convened in June 24, 2013. The members were chosen for their expertise in medical epidemiology, evidence-based medicine, academic affiliations, active clinical practice and research in gastroenterology. Several meetings and consultations were done in order to gather

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specific GERD management concerns of PCPs and gastroenterologists. A review of scientific papers from different accredited training institutions of the Philippine Society of Gastroenterology (PSG) was performed. In addition, an electronic data collection form was circulated to 15 training institutions all over the country to generate current information on demographics, etiology, management and outcomes of consecutive GERD patients seen in their units over a 30-day period in early 2014. A pre-consensus development workshop was held where the results of the surveys and several reviews were presented and discussed. Important issues were identified and forwarded to the core working party for further deliberations. A list of 27 issues, ranging from definition of terminologies related to reflux disease, diagnostic work-up, roles of *H. pylori* (Hp), diet and surgery, first-line and adjuvant treatments for GERD and management of treatment failures and complications were collated and appropriate recommendations were formulated for each issue. Recommendations were based from extensive literature searches of Medline, Embase, the Cochrane Central Register of Controlled Trials and ISI Web of Knowledge, including manual searches in bibliographies of key articles, proceedings of abstracts of major gastroenterology and endoscopy meetings held in the past five years (Asian Pacific Digestive Week (APDW), Digestive Disease Week (DDW) and United European Gastroenterology Week (UEGW) and articles published in the Philippine Journal of Internal Medicine and Philippine Journal of Gastroenterology. Following the modified Delphi process, the 27 recommendations proposed by the core working party were circulated to all training program directors, chiefs of section, and PSG committee chairs for electronic voting by email. Voting for every statement was done as follows; (1) Accept completely; (2) Accept with some reservation; (3) Accept with major reservation; (4) Reject with reservation; (5) Reject completely. Additional comments were encouraged for each statement and revisions made accordingly during subsequent deliberations of the core working party. After the electronic voting, a consensus development conference was held in February 2014 participated in by the training program directors and the core working party. Each participant was assigned to present and defend a statement/recommendation. During the conference, the presenters were required to evaluate appropriate publications, taking special care to include publications from the Philippines and where there are none, papers from Asia were preferred. Robust discussion and debate were encouraged during the consensus development conference and subsequent voting on every statement was conducted anonymously using a wireless keypad system. If the pre-determined agreement of 85% was not achieved, the statement is rejected. The level of evidence and the strength for

each recommendation were rated by the participants using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) process, as follows; a) High — Further research is very unlikely to change our confidence in the estimate of effect b) Moderate — further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate c) Low — further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate d) Very low — any estimate of effect is uncertain. The strength of recommendation was classified as follows; a) strong b) conditional. The participants were constantly reminded that care is needed so as to recognize that 'quality of evidence' is not necessarily synonymous with 'strength of recommendation', and vice versa; and that their informed judgment is necessary.

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PRACTICE GUIDELINE RECOMMENDATIONS:

Recommendation #1:

GERD is a condition resulting from the recurrent backflow of gastric contents into the esophagus and adjacent structures causing troublesome symptoms and/or tissue injury.

Level of agreement: A: 95%, B: 5.0%, C: 0%, D: 0%, E: 0%

GRADE Quality of Evidence: Not applicable

GERD has been described previously through a symptom-based, patient-centered approach and emphasized that GERD symptoms, as they become bothersome and severe, impact negatively the patients' quality of life.¹⁸ During consultation, physicians should assiduously seek out their complaints because patients' description of these disturbing symptoms can be fairly accurate. Recurrent reflux of gastric contents cause injury of the esophageal mucosa, e.g., erosions, strictures, Barrett's metaplasia, and adjacent structures, e.g., reflux laryngitis, dental erosions, etc. Clinical practice guidelines, including this current one, recognize the importance of how the patients perceive and suffer from their symptoms and/or the associated tissue injury in the esophagus and/or adjacent organs resulting from esophagogastric reflux.

Recommendation #2:

A clinical diagnosis of GERD can be made if the typical symptoms of acid regurgitation and/or heartburn are present. In this setting, upper endoscopy is not necessary and empiric acid suppressive therapy can be started in patients without alarm features.

Level of agreement: A: 81.8%, B: 18.2%, C: 0%, D: 0%, E: 0%

GRADE Quality of Evidence: Moderate

Strength of Recommendation – Strong

Heartburn and acid regurgitation are often considered the typical symptoms of GERD and an office diagnosis of GERD may be made when these are present. Heartburn is defined as a burning sensation in the retrosternal area (behind the breastbone) while regurgitation is the perception of flow of refluxed gastric content into the mouth or hypopharynx.¹⁸ Up to 49% of patients with GERD may have heartburn and 42% have acid regurgitation.²⁰ Heartburn and hoarseness are more frequent in men with erosive esophagitis while, acid regurgitation is most common in women.²¹ After a thorough evaluation has failed to document any alarm features, empiric PPI therapy can be started. In both the generalists' and specialists' clinics, PPIs are preferred because of its ready availability, safety, ease of administration, efficacy and cost-effectiveness.¹⁰

The presence of alarm features should trigger a more comprehensive diagnostic approach. These features may include long-standing symptoms more than five years, dysphagia, odynophagia, weight loss, anemia, hematemesis, family history of esophageal adenocarcinoma, nocturnal choking, abdominal mass, recurrent/frequent vomiting, chest pain, etc.²²⁻²⁷

This practice guideline declares that upper endoscopy is not required to make an initial diagnosis of GERD because endoscopy does not add value to the treatment outcome nor influence patients' quality of life. It has a low diagnostic yield, i.e., less than 50% of GERD patients will show positive findings of erosion, Barrett's esophagus (BE) or malignancy.²⁸ The invasive nature of endoscopy, the risks associated with anesthesia and the relatively high cost of the procedure in the Philippines are added concerns.

Recommendation #3:

Patients who present with chest pain, even if suspected to be GERD-related, should undergo an appropriate cardiovascular risk stratification before initiating empiric PPI therapy.

Level of agreement: A: 69.6%, B: 30.4%, C: 0%, D: 0%, E: 0%

GRADE Quality of Evidence: Low

Strength of Recommendation – Strong

Chest pain ultimately diagnosed as associated with coronary artery disease makes up to 40% of all emergency admission while the majority are

non-cardiac chest pain (NCCP). While NCCP is not considered a life-threatening condition, and includes the 42% attributed to GERD, up to 6% of patients with NCCP may have an acute coronary syndrome.³⁰⁻³² In an insurance claims-based study, 29% of malpractice cases for a missed acute myocardial infarction (AMI) in patients presenting with chest pain, including those with NCCP, come from not performing any diagnostic study.³¹

Before starting GERD therapy, patients with chest pain, even if suspected to be NCCP related to GERD must have a thorough initial evaluation of the clinical presentation, a search for history of coronary disease, an electrocardiogram, and troponin I determination.^{31,33,34} Despite the low level of evidence, this CPG favors this more cautious approach. Proper evaluation of patients with chest pain is important not only for correct diagnosis but also for risk stratification.³⁴

While it is recognized that delay may occur in the process, withholding therapy in GERD-related chest pain is not acceptable especially because of the availability of safe and effective short courses of PPI therapy.

Recommendation #4:

NERD refers to the absence of esophageal mucosal lesions on upper endoscopy in patients with typical GERD symptoms and no recent acid suppressive treatment.

Level of agreement: A: 90%, B: 10%, C: 0%, D: 0%, E: 0%

GRADE Quality of Evidence: Not applicable

The diagnosis of non-erosive reflux disease (NERD), as implied in its definition by all current guidelines including this one, can be made only after an upper endoscopy has been performed in patients who have consulted for disturbing symptoms.^{18,33,35-37} During the discussions, we highlighted two important issues when making the diagnosis of NERD, namely; upper endoscopy using conventional white light endoscopes may suffice and patients have not taken acid suppressive medications within the last two weeks. The possibility that mucosal erosions may have been inadvertently healed with easily-accessible over-the-counter medications taken by patients by the time the endoscopy is performed may lead to erroneous inclusion of patients into this category. Newer endoscopes with enhanced imaging capabilities may detect subtle changes suggestive of mucosal injury, however, a recommendation cannot be made until these findings are fully described and validated and until these endoscopes and corresponding expertise are uniformly available throughout the country.

The spectrum of NERD must not include symptoms which are not associated with reflux of gastric contents, e.g., functional heartburn.

Recommendation #5:

Locally-validated standardized questionnaires may be utilized to reinforce the clinical diagnosis of GERD, as well as, to assess response to PPI treatment.

Level of agreement: A: 56.5%, B: 26.1%, C: 17.4%, D: 0%, E: 0%

GRADE Quality of Evidence: Low

Strength of Recommendation - Conditional

Challenges in the diagnosis of GERD led to the development of several non-invasive tools to enable physicians arrive at a fairly accurate and confident clinical assessment of GERD at the point of care, particularly those in the primary care setting. In addition, patient's self-assessment of annoying GERD symptoms and the impact on their quality of life need to be communicated well to their physicians. Several symptom-based questionnaires have been formulated as diagnostic tool so as to ultimately reduce the need for endoscopy and other diagnostic procedures. In the Philippines, the more commonly used questionnaires are Frequency Scale for the Severity of Gerd (FSSG),³⁹ and Gastroesophageal Reflux Disease Questionnaire (GerdQ).^{41,42} Sensitivity and specificity rates ranged from 55%-80% and 54% to 80%, respectively.³⁸⁻⁴⁴ FSSG has been shown to correlate with endoscopic severity of GERD⁴⁴ and assess response to proton pump inhibitor therapy.⁴³ A local validation of the GerdQ has been performed by Castillo-Carandang et al., while Sollano et al. validated the FSSG and utilized the questionnaire in determining treatment response among 1,578 Filipino patients with GERD.^{45,46} In the light of the modest accuracy performance of existing questionnaires, its use cannot be recommended as the sole screening tool for diagnosis of GERD. However, it remains as an important complementary tool for case identification and in disease management.

Recommendation #6:

Further diagnostic plans must take into consideration that the symptoms of GERD, functional dyspepsia and IBS may overlap^a and may coexist with more serious GI disorders, such as, peptic ulcer or gastric cancer.^b

Level of agreement: A: 39.1%, B: 56.5%, C: 4.3%, D: 0%, E: 0%

^a**GRADE Quality of Evidence: High**

^b**GRADE Quality of Evidence: Low**

^a**Strength of Recommendation - Strong**

^b**Strength of Recommendation - Conditional**

Studies among different populations have demonstrated that reflux symptoms occur together with functional dyspepsia and irritable bowel syndrome (IBS). The reported prevalence rates of the concurrence of symptoms of GERD and functional dyspepsia (FD) range from 7.5% to 20.5%.⁴⁷⁻⁵¹ Data suggest that GERD is more prevalent in Western patients with dyspepsia than among South-East Asian dyspeptic patients.⁵²

In a study of 2680 Japanese subjects, 7.7% were diagnosed as having GERD, 10.0% as FD, and 14.2% as IBS. Symptom overlaps were found in 46.9% in GERD, 47.6% in FD, and 34.4% in IBS.⁵³ In 1443 Korean patients, overlap between GERD and dyspepsia, GERD and IBS, and dyspepsia and IBS were observed in 2.3 (95% CI 1.4-3.0), 2.0 (95% CI 1.2-2.6%) and 1.3% (95% CI 0.6-1.8%), respectively. These overlaps occur predominantly in individuals with anxiety.⁵⁴

Up to 62.7% of IBS patients have endoscopic evidence of GERD⁵⁶ while 1.5% of patients with GERD may develop IBS after a 12-month follow up.⁵⁷ Thus, a careful interpretation of patients' complaints should be performed when further diagnostic work-up is contemplated, before starting acid-suppressive therapy or when interpreting treatment outcomes.

On the other hand, there is paucity of data describing a coexistence of GERD and peptic ulcer or gastric malignancy. The clinical presentations of these disorders are also a bit more distinct. However, it must be emphasized that in regions where the prevalence of Hp infection and/or gastric malignancy is high the approach to the diagnosis and management of patients complaining of recurrent GERD symptoms must take these concerns into consideration.

Recommendation #7:

Standard dose PPI once daily for eight weeks, taken 30 minutes before morning meal, is the cornerstone of therapy for erosive esophagitis.

Level of agreement: A: 82.6%, B: 13%, C: 4.3%, D: 0%, E: 0%

GRADE Quality of Evidence: High

Strength of Recommendation - Strong

Proton pump inhibitors (PPIs) have consistently shown better results over Histamine 2 receptor antagonist (H₂RA), antacids, prokinetics and sucralfate in healing rates and symptom relief in both erosive and non-erosive reflux disease.

For erosive esophagitis, a meta-analysis demonstrated superior healing rates are achieved with PPIs compared with H₂RAs, sucralfate, or placebo, i.e., mean overall healing proportion with PPIs vs. H₂RAs or placebo, 84% ± 11%, 52% ± 17%, 28% ± 16%, respectively. Significantly faster healing rate of erosive esophagitis (EE) is also observed with PPIs, i.e., 12%/week, 6.0%/week and 3.0%/week, respectively.²⁹

A recent meta-analysis showed that in studies where NERD was strictly defined by a negative endoscopy and a positive 24-hour pH study, the estimated complete symptom response rate after four weeks of PPI therapy of patients with NERD is comparable to the response rate in patients with ERD, i.e., pooled estimate in patients with ERD was 0.72 (95% CI 0.69-0.74) in 32 studies and 0.73 (0.69-0.77) in two studies which included NERD patients with negative

endoscopy and a positive pH-test. An assessment at eight weeks was not possible because there were no studies which reported complete symptom relief with eight weeks of PPI treatment in NERD.⁵⁸

During the consensus deliberations, a four-week duration of PPI therapy for EE was discussed because it may have economic implications to the GERD patients in the Philippines. Observations from unpublished cohort studies also claim good symptom relief achieved with a short duration of PPI treatment. It was suggested that a well-designed, multicentre study be done among our Filipino patients before a proper recommendation can be made on this regard.

In line with the drugs' pharmacokinetics and pharmacodynamics, traditional delayed-release PPIs are recommended to be administered 30–60 minutes before meals to assure maximal efficacy. Newer PPI formulations with novel dual delayed release delivery system, e.g., dexlansoprazole, can be taken without regard to food and without loss of clinical efficacy for both symptom relief and healing of EE.⁶⁰

Recommendation #8:

Weight reduction and elevation of head of the bed may contribute to symptom improvement.

Level of agreement: A: 82.6%, B: 17.4%, C: 0%, D: 0%, E: 0%

GRADE Quality of Evidence: Moderate

Strength of Recommendation - Conditional

A meta-analysis of nine studies showed that obesity increases significantly the risks for GERD symptoms, erosive esophagitis, and esophageal adenocarcinoma. The risk appears to progressively increase with increasing weight.⁶² A BMI >25 was a significant risk factor for GERD in an Asian study (OR, 1.4; 95% CI, 1.04-1.92).⁶

A systematic review of 16 clinical trials have shown that elevation of the head of the bed and left lateral decubitus position improve the overall time that the esophageal pH is less than 4.0. Weight loss improves pH profiles and symptoms.⁶³ Earlier studies have already shown that weight loss has an independent beneficial effect on symptoms of gastro-oesophageal reflux in patients who are overweight.⁶⁴ In a recent prospective interventional trial involving 332 adults, a structured weight loss program led to complete resolution of GERD symptoms in 65% of subjects and reduction of GERD symptom scores in 81%. In addition, the correlation was significant between percentage of body weight loss and reduction in GERD symptom scores ($r = 0.17$, $P < 0.05$).⁶⁵

It must be noted that adequately powered studies, with long-term follow-up, demonstrating that this reduction in GERD symptoms can be sustained with weight loss are lacking. On the other hand, undesired body weight gain was observed in 36% of 110 Japanese GERD patients on long-term PPI treatment (mean - 2.2

years, range, 0.8-5.7 years).⁶⁶ Although there have been physiologic evidences noted, dietary measures, tobacco and alcohol cessation were not associated with improvement in esophageal pH profiles or GERD symptoms.⁶³

Recommendation #9:

If eight weeks of standard once daily PPI treatment achieved only a partial relief of symptoms, administer the same PPI twice daily or switch to a different PPI.

Level of agreement: A: 76.2%, B: 23.8%, C: 0%, D: 0%, E: 0%

GRADE Quality of Evidence: Moderate

Strength of Recommendation - Conditional

A meta-analysis of 10 studies showed overall benefit, albeit modest, in relief of symptoms and healing of erosive esophagitis among patients who shifted from once-daily omeprazole (20 mg), lansoprazole (30 mg) or pantoprazole (40 mg) to esomeprazole 40 mg for eight weeks.⁵⁹ Several randomized trials showed better improvement of symptoms by increasing the PPI dose to twice daily or by shifting to a different standard dose PPI.^{70,71} Two studies from Japan, which investigated several dose-escalation strategies for patients with PPI-refractory symptoms, demonstrated significantly better symptom relief and healing rates achieved with double dose PPI.^{72,73}

Recommendation #10:

When symptoms relapse after standard GERD treatment, on demand or intermittent PPI therapy is suggested for NERD while, continuous PPI treatment is recommended for moderate to severe erosive esophagitis.^a During maintenance therapy, prescribe the lowest effective dose of PPI.^b

Level of agreement: A: 52.4%, B: 42.9%, C: 4.8%, D: 0%, E: 0%

^aGRADE Quality of Evidence: High

^bGRADE Quality of Evidence: Low

^aStrength of Recommendation - Strong

^bStrength of Recommendation - Conditional

On-demand therapy is PPI consumption when GERD symptoms occur and for as long as the bothersome symptoms persist.⁷⁵ A systematic review of 17 studies showed that NERD patients were more satisfied with this treatment strategy despite consuming a significantly less number of tablets.⁷⁶ It is also effective in patients with mild erosive esophagitis.⁷⁵ Intermittent therapy, on the other hand, is administration of PPI for a pre-defined period of time, usually lasting for five to seven days, even after symptoms have abated.⁷⁵

In a review of 14 studies that compared continuous PPI, intermittent PPI and H₂RAs, only continuous PPI therapy has been shown to maintain healing in more than 75% of patients with six to 12 months of therapy.⁷⁷ Several studies have also shown that remission rates,

as well as, the mean number of days in remission are greater with higher doses of PPIs.^{78,79}

Several guidelines, including this one, advocate using the lowest dose of PPI that alleviates GERD symptoms because of safety concerns.^{33,36} Results of studies comparing standard dose versus low dose PPI in patients with GERD are conflicting.⁸⁰⁻⁸² Defining the lowest effective dose of PPI and the risks and benefits of long-term low dose PPI administration need further study.

Recommendation #11:

Alginate-antacid combination is recommended for relief of episodic and postprandial reflux symptoms.^a Intermittent H2-receptor blockers may be given as alternative to patients intolerant to PPIs.^b

Level of agreement: A: 66.7%, B: 33.3%, C: 0%, D: 0%, E: 0%

^a**GRADE Quality of Evidence: Moderate**

^b**GRADE Quality of Evidence: High**

^a**Strength of Recommendation - Strong**

^b**Strength of Recommendation - Strong**

A gel-like barrier formed by alginates displaces the acid pocket and other non-acidic compounds away from the esophagogastric junction while the antacid portion of the alginate/antacid combination neutralizes gastric acid.⁹⁴⁻⁹⁵ Four trials found the combination superior to placebo in symptom improvement (absolute benefit increase 26%, 95% CI: 12%-41%)⁸³ and, relief of postprandial heartburn may be achieved within 15 minutes in 67% of patients.⁹³

The most common side effects of PPI therapy are headache, diarrhea, constipation, and abdominal pain.⁸⁴ These side effects have been confirmed in some patients via a test-retest strategy but are not significantly higher than placebo.^{84,85} H₂RAs may be used as maintenance therapy for PPI-intolerant patients,⁸⁶ but because tolerance develops during long-term use H₂RAs may be given only intermittently.

Newer 5HT₄ agonists, e.g., mosapride, etc. improve esophageal motility and gastric emptying but are not highly selective and thus, may result in off-target effects that can lead to controversial therapeutic benefits and undesirable adverse reactions.^{87,88}

Recommendation #12:

Refractory GERD pertains to the failure to achieve satisfactory symptom improvement and/or healing of esophagitis in compliant patients treated with PPI twice daily for at least eight weeks.

Level of agreement: A: 59.1%, B: 36.4%, C: 4.5%, D: 0%, E: 0%

GRADE Quality of Evidence: Moderate

Strength of Recommendation - Strong

Approximately, 10-40% of GERD patients on once daily standard dose PPI will remain symptomatic after

eight weeks of therapy.^{67,89-92} Failure of PPI treatment at standard dose, or even at more than standard dose, to resolve GERD-related symptoms is the most common reason for referrals to specialists by the general physicians.⁹³

The current definition of refractory GERD is controversial because many experts consider refractory GERD as a patient-driven phenomenon, however, PPI failure in patients who seek medical attention will exhibit different frequency and/or severity of GERD-related symptoms. As a result, any attempt to narrow the definition of refractory GERD might exclude many true sufferers.⁹⁴ During the consensus deliberations, robust discussions focused also on whether the persistence of unhealed esophageal mucosal breaks be included in the definition of refractory GERD.

The commonalities that exist among the many attempts to define refractory GERD are a) the dose of PPI (once-a-day dose escalated to twice daily due to inadequate response to initial therapy) and b) the period of treatment (ranges from four to eight weeks) before considering that the symptoms are refractory to treatment.^{23,33,95}

In this guideline, we propose that when patient compliance, as well as, correct timing of PPI intake have been ascertained, and appropriate dosing adjustments have been made yet patient symptoms persist and/or esophagitis has failed to heal even on a twice-daily PPI regimen for at least eight weeks then, refractory GERD should be considered.

Recommendation #13:

Ambulatory reflux studies are recommended for patients with refractory GERD who have normal upper endoscopy.

Level of agreement: A: 76.2%, B: 23.8%, C: 0%, D: 0%, E: 0%

GRADE Quality of Evidence: Moderate

Strength of Recommendation - Conditional

Ambulatory reflux monitoring (pH or impedance-pH) is the only test that allows for determining the presence of abnormal esophageal acid exposure, reflux frequency and symptom association with reflux episodes.³⁶ Refractory reflux symptoms represent one of the most common indications for esophageal functional testing.⁹⁶ Patients may be tested 'off' acid-suppressive therapy to confirm or rule out the presence of abnormal acid reflux and/or positive symptom-reflux association. pH studies on patients who are 'on' therapy are performed to determine if gastroesophageal reflux is responsible for persistent symptoms.⁹⁶

Twenty four-hour (24-hr) pH-impedance studies in GERD patients remaining symptomatic even on twice daily PPI have revealed that 50-60% of patients do not have symptoms attributable to reflux, 30-40% have symptoms associated with non-acid reflux and, only

10% are associated with acid reflux.⁹⁷⁻⁹⁹

Combined pH-impedance monitoring is a sound strategy for the evaluation of PPI refractory GERD patients, however, its cost and limited availability in the Philippines have restricted its use. A candid discussion may be initiated with the patient if the test is deemed essential in redirecting the management of GERD patients unresponsive to PPI treatment.

Recommendation #14:

H2-receptor blockers, pain modulators and TLESR reducers may be considered as add-on treatment to PPIs in refractory GERD.

Level of agreement: A: 68.8%, B: 31.2%, C: 4.5%, D: 0%, E: 0%

GRADE Quality of Evidence: Low

Strength of Recommendation – Conditional

A Cochrane Review¹⁰⁰ demonstrated that bedtime H₂RAs can decrease episodes of nocturnal acid breakthroughs (NABs) which can contribute to unsatisfactory response to PPIs (RR 0.48; 95% CI 0.30-0.75). Subgroup analysis, however, gave inconsistent results and the prevalence of NAB was significantly lower in the short term treatment group (RR 0.43; 95% CI 0.25 to 0.72) compared to the long term group.

Baclofen, 10-20mg, three times a day (tid), is effective in reducing TLESRs, decreases significantly upright reflux and regurgitation and, improves over-all symptom scores.^{36,101,102} Side effects such as drowsiness, dizziness and somnolence limit its use. Arbaclofen placarbil, a pro-drug isomer of baclofen, was not superior to placebo in the initial trials.¹⁰³

Citalopram, a selective serotonin reuptake inhibitor, has been studied in patients with hypersensitive esophagus in two recent trials.^{104,105} The latter trial demonstrated that patients with typical reflux symptoms who have failed twice-daily PPI therapy and have a well-defined diagnosis of hypersensitive esophagus will benefit from citalopram.

Recommendation #15:

In the presence of typical GERD symptoms, chronic cough, laryngitis and asthma may be considered extraesophageal manifestations of GERD.

Level of agreement: A: 61.9%, B: 38.1%, C: 0%, D: 0%, E: 0%

GRADE Quality of Evidence: Moderate

Strength of Recommendation – Strong

When laryngitis, cough, and asthma are associated with symptoms of GERD, even when infrequent, they are considered GERD-related syndromes.¹⁸

ASTHMA and GERD

In a systematic review of eight studies (10,491 patients), the pooled sample size weighted-average prevalence of GERD in asthma was 59.2% suggesting a

strong association between GERD and asthma. However, most of the studies included were cross-sectional or case-control trials and therefore, the temporal sequence of these events and conditions cannot be clearly elucidated.¹⁰⁶

A recent meta-analysis of nine RCTs (2,167 patients) demonstrated a small but statistically significant improvement in morning peak expiratory flow (PEF) rate in asthmatic patients given PPIs for a minimum of four weeks.¹⁰⁸

When GERD symptoms are present in patients with frequent asthma attacks, it may be prudent to try empiric PPI therapy. However, it is recommended that patients undergo a thorough investigation for other causative factors if asthma episodes remain uncontrolled.

CHRONIC COUGH AND GERD

The prevalence of chronic cough associated with GERD ranges from 5%-41%. A systematic review of four studies evaluating PPI administration in the symptomatic control of chronic cough demonstrated a trend towards benefit.¹¹⁰ Patients with chronic cough who have GI symptoms consistent with GERD may have a high likelihood of GERD and thus, may be prescribed anti-reflux treatment.¹⁰⁹

LARYNGITIS AND GERD

Laryngopharyngeal reflux is caused by retrograde flow of gastric contents, i.e., acid, pepsin and bile that affect pharyngeal and laryngeal mucosa by direct contact or by a secondary mechanism. A meta-analysis of eight studies showed no statistically significant difference between PPI and placebo in reducing laryngeal symptoms.¹¹¹

Recommendation #16:

In patients with extraesophageal GERD (EeRD) and no alarm features, empiric standard-dose PPI treatment, given twice daily for at least 12 weeks is recommended.

Level of agreement: A: 75%, B: 25%, C: 0%, D: 0%, E: 0%

GRADE Quality of Evidence: Moderate

Strength of Recommendation – Strong

Varying results are shown in trials which evaluated the use of empiric PPI therapy given twice daily (median duration — 12 weeks) for GERD-associated chronic cough,^{110,112,113} laryngitis^{111,114,115} and asthma.^{108,116,117}

The consensus core group modified the assessment of a recent pooled analysis to include only the six articles that enrolled subjects with typical GERD symptoms and found that PPI offers a significant, albeit modest, benefit over placebo.¹¹¹ PPIs also improve morning peak expiratory flow (PEF) among asthmatic patients with or without GERD symptoms but not their quality of life.^{108,117} Furthermore, asthmatic patients with

typical reflux and nocturnal distress had significant improvement in evening PEF.¹¹⁷

In the Philippines, asthma, post-nasal drip and pulmonary tuberculosis are responsible for 33%, 30% and over 20% of cases of chronic cough, respectively. GERD accounts for only less than 4.0%.¹¹⁸ It is therefore prudent to rule out other more common and potentially infectious causes of cough before initiating an empiric PPI therapy.

Recommendation #17:

If empiric PPI fails, a referral to other specialists should be considered. If available, an ambulatory reflux study is also an option.

Level of agreement: A: 70%, B: 30%, C: 0%, D: 0%, E: 0%

GRADE Quality of Evidence: Low

Strength of Recommendation – Strong

In extraesophageal reflux syndromes, acid reflux is rarely the only cause of the patient's symptoms. Multiple therapeutic trials have shown only partial improvement in patients with cough,¹¹⁹⁻¹²¹ laryngitis^{122,123} and asthma.¹²⁴ We recommend a referral to ENT, pulmonary and allergy specialists for patients with extraesophageal reflux disease who remain symptomatic while on double-dose PPI therapy as non-GERD etiologies should be ruled out. In a small group of patients, treatment of cough¹²⁵ or asthma¹²⁶ may help in controlling acid reflux.

Upper endoscopy is not recommended immediately in patients with extraesophageal reflux because of its very low sensitivity.^{127,128} Ambulatory reflux studies, pH and pH-impedance monitoring, also have poor sensitivity in patients with chronic cough,¹²⁹⁻¹³² asthma^{116,133} and laryngitis.¹³⁴ However, pH/impedance testing while on PPI therapy may help identify patients who may need further examinations for other causes of their refractory symptoms.¹³⁵

Recommendation #18:

Endoscopically-suspected Barrett's esophagus must be confirmed by histopathology.

Level of agreement: A: 100%, B: 0%, C: 0%, D: 0%, E: 0%

GRADE Quality of Evidence: High

Strength of Recommendation – Strong

The replacement of the squamous epithelium of the distal esophagus, more than 1.0 cm above the GE junction, by an abnormal columnar epithelium that exhibits specialized intestinal metaplasia determined on histopathological examination of endoscopic biopsies is Barrett's esophagus (BE).¹⁵⁸⁻¹⁶¹ BE increases the risk of distal esophageal adenocarcinoma, although a recent report estimated the absolute annual risk of 0.12%, — much lower than the reported 0.5 from previous studies.¹³⁶

On endoscopy, this guideline recommends the use of the Prague Criteria to determine the most proximal circumferential (C) and maximum extent (M) of the suspected BE from the GE junction. It has shown good utility across ethnicity and high overall validity, even among trainees.¹³⁷⁻¹⁴⁰ Targeted biopsies using endoscopes with enhanced imaging technologies, e.g., narrow band imaging, is encouraged because it significantly increases the diagnostic yield for intestinal metaplasia, dysplasia or carcinoma.¹⁴¹

Recommendation #19:

PPI treatment causes regression of Barrett's esophagus and may reduce the risk of progression to high-grade dysplasia and adenocarcinoma

Level of agreement: A: 65%, B: 35%, C: 0%, D: 0%, E: 0%

GRADE Quality of Evidence: Moderate

Strength of Recommendation – Strong

A double blind RCT in 1999 demonstrated that PPI treatment leads to BE regression.¹⁴² A prospective multicenter cohort study of 540 BE patients (mean follow-up — 5.2 years) reported a reduction in the risk of neoplastic progression with PPI use.¹⁴⁵ Prolonged and good adherence to PPI use were associated with a positive effect. A retrospective observational study in 2010, utilizing prescription information of pharmacy records, showed that PPI therapy reduces the risk of neoplasms in patients with BE.¹⁴⁴ Meanwhile, a case-control study among 9,883 newly diagnosed BE, reported no cancer protective effects from PPIs, i.e., relative risk of high grade dysplasia and adenocarcinoma was 2.2 (0.7-6.7) and 3.4 (1.1-10.5) in long low- and high-adherence PPI users, respectively. The authors cautioned that the increased risks may not be due solely to the true negative effect of PPI but maybe due to confounding by indication.¹⁴⁷

It is proposed that PPIs protect against cancer progression through their anti-inflammatory and immunomodulatory effects on the interactions with neutrophils, monocytes, endothelial and epithelial cells; and preventing adhesion molecule binding in malignant cells.¹⁴⁶

Recommendation #20:

Endoscopic surveillance of patients with Barrett's Esophagus may lead to early detection of high-grade dysplasia and/or adenocarcinoma.

Level of agreement: A: 71.4%, B: 23.8%, C: 4.8%, D: 0%, E: 0%

GRADE Quality of Evidence: Moderate

Strength of Recommendation – Strong

Chronic gastroesophageal reflux may lead to the development of metaplastic Barrett's epithelium with potential progression in a stepwise fashion to dysplasia and invasive esophageal adenocarcinoma.¹⁴⁸

Pooled data from two meta-analyses showed that the incidence of esophageal cancer among patients with BE is 0.41% and 0.63% per year, respectively.^{149,150} The pooled mortality rate is 0.3% per year.⁶ Although mortality from esophageal cancer among patients with BE would be expected to be higher than in the general population, a large epidemiologic study indicated that only 4.7% of deaths among patients with BE was accounted for by esophageal cancer.¹⁵¹ The recent Danish study estimated a much lower absolute annual cancer risk of 0.12% in BE patients, adding further controversy to the debate on the value of endoscopic surveillance.¹³⁶

Endoscopic surveillance for BE may have the theoretical advantage of identifying early-stage esophageal carcinoma meant to decrease mortality, however, such programs are not yet based on strong and robust evidence. Furthermore, it carries profound resource and financial implications.

Recommendation #21:

Long-term administration of PPI is safe; however, careful consideration is needed in patient groups at risk for complications.

Level of agreement: A: 85.7%, B: 14.3%, C: 0%, D: 0%, E: 0%

**GRADE Quality of Evidence: Moderate
Strength of Recommendation – Strong**

Proton pump inhibitors (PPIs) are generally safe but associated adverse events from long-term use have generated concerns, i.e., vitamin B12 deficiency; iron deficiency; increased susceptibility to pneumonia, enteric infections, and fractures; and drug interactions.^{152,153}

Gastric acid and pepsin are required to release cobalamin from dietary protein, as well as, in the absorption of dietary non-heme iron. Two recent reviews, however, did not show supporting clinical evidence of B₁₂ and iron deficiency among chronic users of PPI.^{152,153} Earlier case-control studies showed an increased incidence of hip and osteoporosis-related fractures^{154,155} especially in individuals with at least one other risk factor present.¹⁵⁷ However, analysis of the Manitoba Bone Mineral Density Database concluded that the association between PPI use and hip fracture was probably due to other risk factors independent of osteoporosis.¹⁵⁶ A recent meta-analysis demonstrated a modest increase in risk (OR 1.25) for hip fracture but was limited by substantial heterogeneity among the studies included.¹⁵⁸

A systematic review of observational studies, and a cohort study of 100,000 discharges in tertiary care revealed that both PPI and H₂RA use are associated with an increased risk of *C. difficile* and other enteric pathogen infection.¹⁶⁰ In addition, systematic reviews and meta-analyses found also an increased

susceptibility among PPI users to *Salmonella* (RR ranging from 4.2 to 8.3), *Campylobacter* (RR 3.5-11.7), and *C. difficile* (RR 1.2-5.0) infections¹⁶¹, pneumonia¹⁹⁶ and, community-acquired pneumonia¹⁹⁷. Other studies have also demonstrated increased risk of community-acquired (CAP) associated with high dose, short-term PPI usage.^{162,163} It must be noted, however, that these analyses are confounded by significant heterogeneity.

Recommendation #22:

When clinically warranted, short term PPI treatment is an option in the last two trimesters of pregnant women with GERD.

Level of agreement: A: 85.7%, B: 14.3%, C: 0%, D: 0%, E: 0%

**GRADE Quality of Evidence: Moderate
Strength of Recommendation – Strong**

Lifestyle modifications, e.g., elevation of the head part of the bed and avoiding heavy meals especially at night, may help alleviate GERD symptoms associated with pregnancy. H₂RAs, notably ranitidine, as well as antacids (except sodium bicarbonate-containing preparations) have been studied extensively and has a well-established efficacy and safety in pregnancy.^{164,165}

The US FDA has labelled all PPIs as Class B drugs (animal studies show no risks, no human studies done), except for Omeprazole (Class C). In the general population, the incidence of major fetal malformations is approximately 1.0%-3.0%.¹⁶⁶ A meta-analysis noted that there is no increased risks for major fetal abnormalities (OR 1.12, 95%CI 0.86 – 1.45), spontaneous abortion (OR 1.29, 95%CI 0.84 – 1.97) and pre-term deliveries (OR 1.13, 95%CI 0.96 – 1.33) associated with PPI use in pregnancy.¹⁶⁷

It is prudent to engage the pregnant patient in a candid discussion regarding the risks and benefits of PPI intake before prescribing these medications.

Recommendation #23:

Screening and treatment of *Helicobacter pylori* infection is not performed routinely in the management of GERD.

Level of agreement: A: 95%, B: 5%, C: 0%, D: 0%, E: 0%

**GRADE Quality of Evidence: High
Strength of Recommendation – Strong**

In the Philippines, however, where the prevalence of the infection is high, when endoscopy is indicated and subsequently performed, testing for and subsequent eradication of Hp infection is recommended.

Current Hp guidelines declare that Hp eradication does not cause GERD nor does it affect the outcome of PPI therapy in GERD thus, routine testing for Hp is not recommended in GERD¹⁶⁹

Guidelines from the Asia Pacific¹⁷⁰ and the World Gastroenterology Organisation¹⁷¹ have underlined the

high prevalence of Hp infection in the developing world and its role in gastric carcinogenesis. Several RCTs and meta-analyses have shown that eradication of Hp significantly reduces the risk of gastric cancer.¹⁷²⁻¹⁷⁶

The Hp prevalence in peptic ulcer patients seen at a tertiary hospital in Manila is high, i.e., 76.6% in 1996, and 33.48% in 2002.¹⁷⁷ In Cebu, the prevalence was 43% in 2008. Gastric cancer also remains a major health issue in the country. As of 2010, it is the seventh most common cause of cancer deaths in the Philippines.¹⁷⁸

In view of the high prevalence of Hp infection in the Philippines and its attendant risks for gastric cancer and peptic ulcer disease, it is recommended to test for and treat Hp infection when the opportunity presents during patients' consultation for their GERD symptoms.

Recommendation #24:

Upper endoscopy is not required to make a diagnosis of GERD.

Endoscopy is recommended only in these circumstances, as follows;

A. At initial consultation:

1. presence of alarm features
2. with risk factors for BE

B. During treatment:

1. new-onset alarm symptoms

C. After treatment:

1. after 12 weeks of PPI therapy for moderate to severe esophagitis
2. partial or no symptom response after at least eight weeks of twice daily PPI therapy in refractory GERD
3. unsatisfactory symptom relief after at least 12 weeks of twice daily PPI therapy in extraesophageal GERD (EeRD)

D. As part of the work-up prior to contemplated anti-reflux surgery

Level of agreement: A: 76.5%, B: 23.5%, C: 0%, D: 0%, E: 0%

GRADE Quality of Evidence: Low

Strength of Recommendation - Conditional

When the clinical presentation includes acid regurgitation and/or heartburn, this guideline strongly recommends that the diagnosis of GERD can be made right in the physician's office. This clinical diagnosis can be reinforced further by using concomitantly a locally-validated GERD questionnaire. Thus, upper endoscopy is not an important first step in the index diagnostic evaluation. However, when alarm features, e.g., dysphagia, bleeding, anemia, weight loss, and recurrent vomiting are present an upper endoscopy is indicated.²⁵

Upper endoscopy is also indicated if the patient has risk factors for BE. Well-established risk factors for BE include advanced age, male sex, white race, GERD, hiatal hernia, elevated BMI, and a predominantly intra-

abdominal distribution of body fat.^{23,179} Age >40 years ($p = 0.008$), presence of heartburn or acid regurgitation ($p = 0.03$), and heartburn more than once a week ($p = 0.007$) are all independent predictors of the presence of BE.¹⁸⁰

Even when suspected, BE and associated dysplasia can be missed in the presence of inflammation; therefore, repeat evaluation should be considered after complete healing of esophagitis.¹⁸¹ In 172 patients with EE without BE on initial endoscopy, BE was suspected in 32 and confirmed in 16 patients (13.8%) on repeat endoscopy after EE has healed.¹⁸² Severe esophagitis is associated with a higher rate of detection for BE when mucosal healing occurs.²²⁵

After a course of acid-suppressive therapy and satisfactory symptom resolution has not been achieved, we recommend an upper endoscopy to assess mucosal healing and to search for a different diagnosis, e.g., eosinophilic esophagitis. It may be performed with ambulatory pH monitoring and other studies to further assess failure of therapy. Lastly, it is also performed prior to contemplated anti-reflux surgery in exasperated patients.¹⁸³

Recommendation #25:

Surgery, preferably laparoscopic fundoplication done in high-volume, expert centers, is an option only among patients with GERD whose symptoms respond to PPI therapy but not amenable to long-term medical treatment.

Level of agreement: A: 82.4%, B: 17.6%, C: 0%, D: 0%, E: 0%

GRADE Quality of Evidence: High

Strength of Recommendation - Strong

Patients who are not amenable to long-term medical treatment, presence of a large hiatal hernia, severe GERD complications and, refractory GERD may be offered surgery. Laparoscopic fundoplication has replaced open anti-reflux surgery as the procedure of choice due to better short-term outcomes. A Cochrane review of four RCTs involving 1,232 patients showed significant improvements in symptoms of heartburn, reflux and bloating.¹⁸⁴

In an open-parallel 12-year long-term follow-up of patients randomized to omeprazole or fundoplication,¹⁸⁵ the surgical group had a significantly better control of overall disease manifestation as compared to the medical group (53% vs. 45% at $p=0.02$). However, post-fundoplication adverse events, such as, bloatedness, inability to belch and dysphagia may be found in 15-20% of patients.¹⁸⁵⁻¹⁸⁷ In two recent meta-analyses,^{188,189} partial fundoplication significantly resulted to lower prevalence of inability to belch and dysphagia as compared to total fundoplication.

It is noted that the success of surgery is highest among patients who present with typical symptoms of

GERD and who have demonstrated a good response to PPI therapy.¹⁹⁰ Crucial to the success of surgery is the expertise of the surgical team and of the center where it is performed.

Recommendation #26:

Esophageal manometry and ambulatory reflux studies should be performed prior to surgery to exclude disorders other than GERD.

Level of agreement: A: 75%, B: 25%, C: 0%, D: 0%, E: 0%

GRADE Quality of Evidence: Low

Strength of Recommendation – Strong

Esophageal manometry and reflux studies are not absolutely necessary during the index diagnostic work-up of reflux disease because of their limited utility.^{36,183,193} Moreover, both procedures are not readily available in the Philippines. However, esophageal manometry must be performed prior to contemplated antireflux surgery to rule out alternative diagnoses other than GERD, i.e., achalasia, scleroderma, non-reflux induced esophageal spasm, and other diseases where surgery has limited or no benefit.^{36,183,193} When combined with ambulatory pH studies, the diagnostic documentation for gastroesophageal reflux improves further.^{36,194} Post-operatively, pH impedance studies may have a role in the assessment of outcomes with fundoplication.¹⁹⁵

Recommendation #27:

Endoluminal treatments for GERD should be performed only in the setting of a clinical trial.

Level of agreement: A: 58.3%, B: 33.3%, C: 8.3%, D: 0%, E: 0%

GRADE Quality of Evidence: Moderate

Strength of Recommendation – Strong

Endoluminal treatments aim to increase LES basal pressure, decrease transient lower esophageal sphincter relaxations (TLESRs) or decrease acid reflux events. The first generation endoluminal treatments, e.g., endoscopic gastroplication (Endocinch), radiofrequency energy, and submucosal bulking/copolymer (Enteryx) injection into the LES were technically easy to perform but severe complications, marginal short-term efficacy and lack of durability of response were major issues which led to its early demise.¹⁹⁶⁻²⁰⁰

Recently-developed devices, like titanium beads implantation (LINX) and full thickness plication (Esophyx) have shown promising results. The LINX system have shown significant reduction in esophageal pH and acid exposure, daily PPI intake and improved GERD HRQoL off PPIs in up to four years of follow-up.²⁰¹⁻²⁰³

Radiofrequency ablation (RFA) of Barrett's epithelium achieve 81% and 90.5% eradication of low-grade and high-grade dysplasia, respectively. The incidence of post-procedure buried metaplasia and complications, e.g., stricture are also low.^{204,205}

Conclusions

The symptoms of GERD are troublesome, recurrent and annoying thus prompting patients to consult often and take medications for a considerable duration. These symptoms diminish their quality of life and affects negatively their work and productivity. When the typical clinical presentation is present a clinical diagnosis of GERD can be made in the physician's office and an empiric PPI treatment may be started even without performing an upper endoscopy, most especially in those with no alarm features. In this guideline, the indications of upper endoscopy in GERD is well articulated and we encourage all practitioners to exercise careful attention when recommending the procedure to GERD patients. PPIs remain the cornerstone of treatment for erosive esophagitis and several strategies are recommended for those whose symptoms do not respond completely, i.e., switching to another PPI or doubling the dose of the currently-administered PPI. The pathophysiology of the extraesophageal manifestations of GERD is still poorly understood. PPI therapy in these patients will often reduce their GERD symptoms but not as efficiently their extraesophageal symptoms. Adjuvant therapies are recommended to relieve bothersome, episodic GERD symptoms. Most endoluminal forms of treatment have not shown durable long-term benefits. The recommendation/s on the role of ambulatory pH monitoring are described well and is tempered by the realization that these facilities are still very few in the country and thus, currently cannot be accessed easily by our GERD patients. Given that Hp infection is still highly prevalent in the Philippines, we recommend that an opportunistic testing for Hp be performed on GERD patients, whenever the occasion presents. A histologic confirmation of Barrett's epithelium is emphasized and targeted biopsies during endoscopic surveillance can lead to early detection of high-grade dysplasia and early adenocarcinoma.

These recommendations are aimed to improve patient care and ensure better treatment outcomes. They are based on scientific evidences accessible currently to the authors and thus, we are aware that future studies may affirm or effect a modification of these recommendations. In addition, there may be clinical situations where these guidelines may not be applicable and thus, we encourage physicians to exercise good clinical judgment when using it as reference. We are committed to update this document if and when future published evidence will have created a major impact on our confidence regarding the recommendations included herein.

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