







## REVIEW ARTICLE

# Thailand guideline 2020 for medical management of gastroesophageal reflux disease

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**Abstract**

Gastroesophageal reflux disease (GERD) is one of the most prevalent and bothersome functional gastrointestinal disorders worldwide, including in Thailand. After a decade of the first Thailand GERD guideline, physician and gastroenterologist encountered substantially increase of patients with GERD. Many of them are complicated case and refractory to standard treatment. Concurrently, the evolution of clinical characteristics as well as the progression of investigations and treatment have developed and changed tremendously. As a member of Association of Southeast Asian Nations, which are developing countries, we considered that the counterbalance between advancement and sufficient economy is essential in taking care of patients with GERD. We gather physicians from university hospitals, as well as internist and general practitioners who served in rural area, to make a consensus in this updated version of GERD guideline focusing in medical management of GERD. This clinical practice guideline was constructed adhering with standard procedure. We categorized the guideline in to four parts including definition, investigation, treatment, and long-term follow up. We anticipate that this guideline would improve physicians' proficiency and help direct readers to choose investigations and treatments in patients with GERD wisely. Moreover, we wish that this guideline would be applicable in countries with limited resources as well.

**Introduction**

Gastroesophageal reflux disease (GERD) is a bothersome condition that cause physical, emotional, and economic burden worldwide. In Thailand, the prevalence of GERD has been reported as 7.4% of those affected by heartburn and/or acid regurgitation among a general population cohort of 3120<sup>1</sup> and even higher in asthmatic patients, at 37.50% (21 of 56 patients).<sup>2</sup> When using a questionnaire to determine symptoms of 2488 patients who underwent upper gastrointestinal endoscopic examination, typical reflux symptoms were found in 855 participants (34.4%), 143 had only reflux symptoms, and 712 had overlapping symptoms of GERD and dyspepsia.<sup>3</sup> In a survey from the Asia Pacific region of 450 patients who were diagnosed with GERD and under treatment with proton pump inhibitors (PPIs),

76% reported a negative impact on well-being.<sup>4</sup> The Thailand GERD guideline has been developed to update the statements, rationales, levels of evidence, and grades of recommendation for the management of GERD. The ultimate goal of the guideline is to update the knowledge gathered and provide practical management for general practitioners and internists in the care of Thai patients, while also being applicable to similar settings in other countries, especially those in regions with limited resources. A panel composed of 24 experts, 1 general practitioner, and 1 internist was gathered from around the country to review and evaluate updated evidence regarding GERD. The guideline mainly addresses four issues: (i) evaluation and diagnosis, (ii) investigation, (iii) treatment, and (iv) long-term follow up and management of GERD.

## Method

The guideline was processed in accordance with Grading of Recommendations, Assessment, Development, and Evaluation (GRADE).<sup>5</sup> Prior to the first meeting, a survey questionnaire regarding the knowledge, understanding, and needs of physicians regarding GERD was sent out, which was filled in and returned by 230 responders, mainly general practitioners.

**First consensus meeting (July 19–20, 2019).** The first face-to-face meeting was aimed to develop the proper clinical questions. Twenty-six committee members divided into four working groups, each responsible for (i) evaluation and diagnosis, (ii) investigation, (iii) treatment, and (iv) long-term follow up and management of GERD. The panel was composed of experts in gastroenterology who represent the university hospitals. Also included were a general practitioner and an internist. The Problem/Population, Intervention, Comparison, and Outcome method was adopted to identify the appropriate clinical questions regarding the results of the survey and additional updated essential information. Finally, 26 preliminary clinical questions were proposed by the working groups. Over the subsequent 3 months, the systematic literature search for each statement was conducted from scientific database, including Ovid, MEDLINE, Embase, and Cochrane library and included only eligible English publications. The formulated statements from systematic review were provided to all members for discussion via internet platform over 4 months before the final meeting.

**Second (final) consensus meeting (November 15–16, 2019).** All clinical statements were displayed and discussed in a face-to-face manner. For individual clinical statements, the assigned members of each working group presented the evidence to support the statement. The level of evidence and strength of recommendation were determined in accordance with the Grading of Recommendations, Assessment, Development, and Evaluation.<sup>5</sup> Clinical practicality and cost effectiveness were taken into account. The discussion and justification of the statements were thrown open, and agreement was reached through a power vote with blinded voters. The consensus “recommend” was achieved when at least 80% of voting members declared “strongly agree” or “agree.” If the consensus was not reached, the panelists discussed the statement again with a view to its modification, followed by a second round of voting. If consensus was still not reached, the statement was discussed and adjusted again, and then, a third round of voting was conducted. If the statement was still unable to achieve the consensus at the third voting, that statement was rejected. Additionally, “strongly recommend” was realized only if 80% or more of the voting members specified “strongly agree.” Otherwise, the strength of the recommendation for these statements was defined as “suggest” or “conditional recommendation.”

Ultimately, a total of 22 consensus statements were realized (Table 1). All of the statements and rationales were gathered and written by a secretary and proofread by the chairperson of each working group. All final approved statements, rationales, levels of evidence, and grades of recommendation are summarized in this guideline. Algorithms for the management of GERD are also proposed (Figs 1 and 2).

## Definitions of terms used in the present guideline.

For proper utilization of the guideline, agreement on definitions is mandatory. The definitions used in this guideline are as follows.

- 1 Gastroesophageal reflux disease, according to the Montreal classification,<sup>6</sup> is a condition that develops when reflux of stomach contents causes troublesome symptoms and/or complications. The refluxate can be acid, base, or gas. The troublesome symptoms are typically heartburn or retrosternal burning and regurgitation. Dysphagia is also possible, although rare. Furthermore, GERD can be categorized into esophageal syndrome and extraesophageal syndrome.
  - 1.1 Esophageal syndrome consists of heartburn, regurgitation and reflux chest pain syndrome, or noncardiac chest pain. Furthermore, those affected also include patients who might have no symptoms but have sequelae of acid reflux detected by endoscopic findings including reflux esophagitis, esophageal stricture, Barrett’s esophagus, and esophageal adenocarcinoma.
  - 1.2 Extraesophageal syndrome is a clinical condition caused by GERD or associated with GERD but with atypical GERD symptoms. The established associations include reflux cough syndrome, reflux laryngitis syndrome, reflux asthma syndrome, and reflux dental erosion. Pharyngitis, sinusitis, idiopathic pulmonary fibrosis, and recurrent otitis media syndrome are also considered as potential causes of GERD, although their association remains equivocal. Hence, other possible causes of these clinical syndromes should be addressed before diagnosing GERD.
- 2 Bothersome symptoms are defined as symptoms related to GERD that are severe enough to compromise the patient’s daily life and activity. In general, if the symptoms are mild but occur at least 2 days per week, or if the symptoms develop only 1 day per week but are severe, they are considered bothersome.
- 3 Alarm features<sup>7–9</sup> are defined as any clinical features that indicate further evaluation to seek out other diagnosis other than GERD or its complications (e.g. dysphagia, gastrointestinal bleeding, anemia, involuntary weight loss, recurrent vomiting, and odynophagia).
- 4 Standard dose of PPI represents the dosage of PPIs recommended for use in the treatment of GERD.<sup>10</sup>
- 5 PPI-nonresponsive GERD is defined as GERD symptoms that do not respond to a standard-dose regimen of PPI in a 4- to 8-week period.
- 6 PPI-refractory GERD is defined as GERD symptoms that do not respond to a high dose or double dose of PPI in an 8- to 12-week period.
- 7 On-demand therapy is defined as use of PPIs to control GERD symptoms only when symptoms develop.
- 8 Maintenance therapy is defined as taking PPIs daily to control GERD symptoms.

**Clinical question 1:** Are typical reflux symptoms alone without alarm features enough to diagnose GERD?

**Statement 1:** GERD can be diagnosed with no requirement of additional investigations if the patient presents with typical GERD symptoms (heartburn and acid regurgitation) and no alarm features upon normal physical examination.

**Table 1** Summary and strength of recommendations

## Part I: Evaluation and diagnosis

Statement 1: Gastroesophageal reflux disease (GERD) can be diagnosed with no requirement of additional investigations if the patient presents with typical GERD symptoms (heartburn and acid regurgitation) and no alarm features upon normal physical examination. Level of evidence: Moderate Grade of recommendation: Conditional recommendation

Statement 2: In patients who have symptoms of GERD with coexisting alarm features, EGD is indicated. Level of evidence: High Grade of recommendation: Conditional recommendation

Statement 3.1: Patients with extraesophageal symptoms of GERD without alarm features can be diagnosed as GERD after excluding other conditions/diseases. Level of evidence: Low Grade of recommendation: Conditional recommendation

Statement 3.2: Careful cardiac evaluation is needed before diagnosing noncardiac chest pain (NCCP) from GERD. Level of evidence: Moderate Grade of recommendation: Conditional recommendation

Statement 4: Patients with typical reflux symptoms without alarm features can be diagnosed as GERD if they respond to a 2-week PPI trial. Level of evidence: Very low Grade of recommendation: Conditional recommendation

## Part II: Investigation

Statement 5: Upper endoscopy is recommended for refractory GERD if patients fail to respond to PPI therapy optimization. Level of evidence: Low Grade of recommendation: Conditional recommendation

Statement 6.1: Screening and treatment of *Helicobacter pylori* infection are not generally recommended in GERD patients. Level of evidence: High Grade of recommendation: Conditional recommendation

Statement 6.2: In GERD patients who require long-term PPI treatment, *Helicobacter pylori* screening and treatment should be considered for the prevention of progression of gastric histopathology to corpus atrophy or intestinal metaplasia. Level of evidence: Moderate Grade of recommendation: Conditional recommendation

Statement 7: We are against routinely random esophageal biopsy in refractory GERD patients who have no esophageal injury proven by EGD. Esophageal biopsy should be performed only in refractory GERD patients who have clinical or endoscopic findings suggestive of eosinophilic esophagitis. Level of evidence: Low Grade of recommendation: Conditional recommendation

Statement 8: Esophageal manometry and/or esophageal pH monitoring should be considered in PPI-refractory GERD patients when the result of EGD is negative. Level of evidence: Moderate Grade of recommendation: Conditional recommendation

## Part III: Treatment

Statement 9.1: Weight reduction is recommended for GERD patients who are overweight or have recent weight gain. Level of evidence: Moderate Grade of recommendation: Conditional recommendation

Statement 9.2: Cessation of tobacco smoking and alcohol consumption are recommended for GERD patients. Level of evidence: Moderate Grade of recommendation: Conditional recommendation

Statement 9.3: Restraint from food for 3 h before bedtime and consideration of head-of-bed elevation are recommended for GERD patients with nocturnal symptoms. Level of evidence: Moderate Grade of recommendation: Conditional recommendation

Statement 10: Standard-dose PPI for 4–8 weeks has more efficacy for the control of symptoms of GERD than histamine type 2 receptor antagonists and antacids. PPI is recommended as first-line treatment for GERD. Level of evidence: High Grade of recommendation: Conditional recommendation

Statement 11: Although PPIs twice daily show no significant difference in symptomatic relief of heartburn compared with PPIs once daily in clinical trials, increasing the dose of PPI before further investigations in PPI-non responsive GERD is beneficial in an inadequate acid control GERD patient. Level of evidence: High Grade of recommendation: Conditional recommendation

Statement 12: Switching PPIs in patients with PPI-nonresponsive GERD was as effective as increasing the PPI dosage to twice a day for the control of heartburn symptoms. Level of evidence: Moderate Grade of recommendation: Conditional recommendation

Statement 13.1: Addition of short-term prokinetics to PPI therapy in PPI-nonresponsive GERD patients shows a tendency toward GERD symptom improvement. Level of evidence: Moderate Grade of recommendation: Conditional recommendation

Statement 13.2: There is limited evidence for or against the combination of PPI and alginate as an adjunctive treatment of nonresponsive GERD. Level of evidence: Moderate Grade of recommendation: Conditional recommendation

Statement 13.3: There is limited evidence for against the combination of PPIs and neuromodulators as an adjunctive treatment in nonresponsive GERD patients. Level of evidence: Moderate Grade of recommendation: Conditional recommendation

Statement 14: High-dose PPI increases symptom relief of GERD-related NCCP. Level of evidence: Moderate Grade of recommendation: Conditional recommendation

Statement 15: Treatment with PPI showed promising benefits in established extraesophageal GERD symptoms, especially in patients who also had typical symptoms of GERD. Level of evidence: Low Grade of recommendation: Conditional recommendation

Statement 16: There is inadequate or limited supporting evidence for the use of other add-on medication such as prokinetics, baclofen, gabapentin, or alginate for established extraesophageal GERD patients who do not respond to PPI treatment. Level of evidence: Low Grade of recommendation: Conditional recommendation

## Part IV: Long-term follow up

Statement 17: In GERD patients who had complete response to initial treatment, either step-down or on-demand therapy provide similar efficacy for symptoms control. Level of evidence: Moderate Grade of recommendation: Conditional recommendation

Statement 18: Continuous PPI therapy is effective in GERD patients with severe erosive esophagitis, and/or severe/frequent recurrence of symptoms. Level of evidence: Low Grade of recommendation: Conditional recommendation

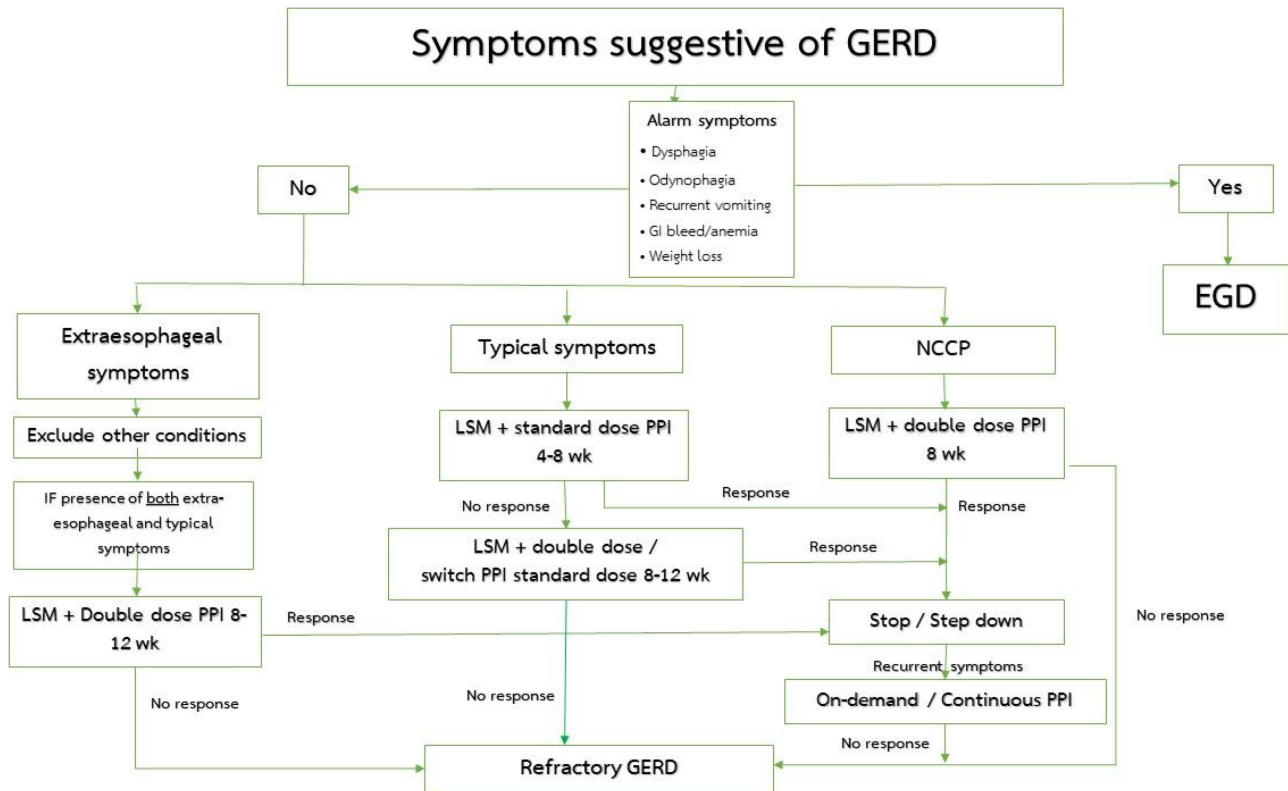
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Statement 19: PCAB is effective and noninferior to PPIs for healing and maintenance of healed EE. In addition, PCABs have a trend toward higher healing rates than PPIs in patients with severe EE. Level of evidence: High Grade of recommendation: Conditional recommendation

Statement 20: In patients with EE, combination treatment of PPIs with other medications including prokinetics, rebamipide, and alginates, has been shown to be more effective than PPI alone in improving GERD symptoms. However, no convincing evidence that such combinations are better than PPI monotherapy for the healing of EE has been demonstrated. Level of evidence: Moderate Grade of recommendation: Conditional recommendation

Statement 21: Long-term PPI use may reduce esophageal cancer risk in patients with Barrett’s esophagus. We recommend that patients be referred to a specialist. Level of evidence: Low Grade of recommendation: Conditional recommendation

EE, erosive esophagitis; PCAB, potassium competitive acid blocker; PPI, proton pump inhibitor.



**Figure 1** Algorithm of management for patients with symptoms suggestive of GERD. EGD, esophagogastroduodenoscopy; GERD, gastroesophageal reflux disease; GI, gastrointestinal; NCCP, noncardiac chest pain; LSM, life style modification; PPI, proton pump inhibitor.

Level of evidence: Moderate  
Grade of recommendation: Conditional recommendation

**Rationale**

Typical symptoms of GERD<sup>11,12</sup> have been defined as heartburn and acid regurgitation. Both symptoms are common presenting symptoms of GERD that can be found in up to 82.4% and 58.8% of patients, respectively.<sup>13</sup> Heartburn is more specific to GERD than acid regurgitation,<sup>13</sup> with sensitivity and specificity for diagnosing GERD of 78% and 60%, respectively.<sup>14</sup> Although studies have shown that these typical symptoms produce a positive test by 24-h esophageal pH monitoring in only 40–50%,<sup>15,16</sup> these symptoms are still used in many standard guidelines<sup>11,12,17</sup> because of its simplicity and practicality. Hence, further investigations (esophagogastroduodenoscopy [EGD] and/or 24-h esophageal pH monitoring) are not yet necessary in patients with no alarm features and normal physical examination before PPI trial.

**Clinical question 2:** When should EGD be promptly performed for patients with GERD symptoms?

**Statement 2:** In patients who have symptoms of GERD with coexisting alarm features, EGD is indicated.

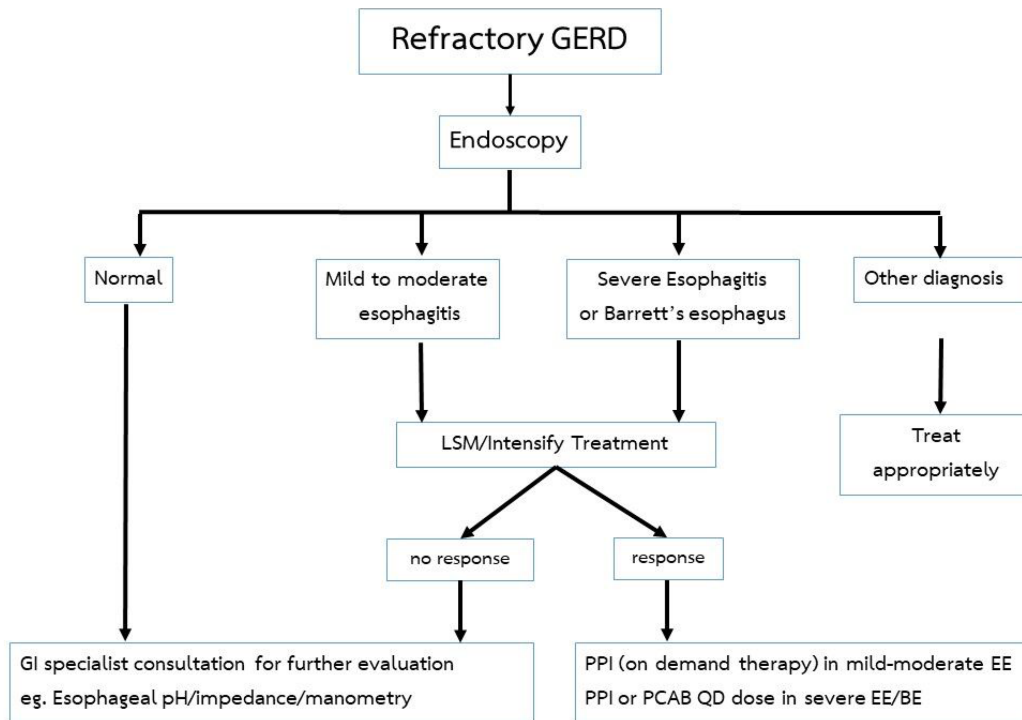
Level of evidence: High  
Grade of recommendation: Conditional recommendation

**Rationale**

Many studies have demonstrated that in patients with clinical symptoms of GERD, alarm features are related to esophageal complications.<sup>7–9,18–22</sup> In particular, involuntary weight loss (84%), dysphagia (85%), and anemia (95%) are strongly associated with esophageal complications.<sup>18</sup> Therefore, general international guidelines recommend performing EGD before commencing treatment of GERD.<sup>8,18,19,22–24</sup>

Barrett’s esophagus, a premalignant lesion of esophageal adenocarcinoma, has been shown to be associated with some risk factors





BE =Barrett’s esophagus, EE = erosive esophagitis, GERD = gastroesophageal reflux disease, GI = gastrointestinal, LSM = lifestyle modification, PCAB = potassium competitive acid blocker, PPI = proton pump inhibitor, QD = once daily

**Figure 2** Algorithm of management for patients with refractory GERD. BE, Barrett’s esophagus; EE, erosive esophagitis; GERD, gastroesophageal reflux disease; GI, gastrointestinal; LSM, lifestyle modification; PCAB, potassium competitive acid blocker; PPI, proton pump inhibitor; QD, once daily.

in patients, especially chronic GERD of 5 years’ duration, age 50 years or older, nocturnal reflux symptoms, hiatal hernia, body mass index more than 25, and tobacco use. Therefore, many guidelines suggest an EGD for patients at risk.<sup>8,9,19,21,23,25</sup> However, an Asian study found very low prevalence of Barrett’s esophagus (1–2%) except in Japan and India, all of which were short-segment and thus with very low risk for progression to esophageal adenocarcinoma. Hence, the committee suggests not to perform EGD routinely in the Thai population unless the coexist with alarm symptoms.<sup>26</sup>

**Clinical question 3:** Could patients with extraesophageal symptoms of GERD be diagnosed as solely GERD based on symptoms?

**Statement 3.1:** Patients with extraesophageal symptoms of GERD without alarm features can be diagnosed as GERD after excluding other conditions/diseases.

Level of evidence: Low

Grade of recommendation: Conditional recommendation

**Rationale**

In most cases, patients with laryngitis or asthma as extraesophageal GERD usually have typical reflux symptoms.<sup>6</sup> A prospective observational study of 16 patients with hoarseness from extraesophageal GERD reported that this symptom improved significantly after taking a high dosage of PPI (omeprazole 40–80 mg/day for 6 weeks) and relapsed after PPI discontinuation.<sup>27</sup> Two randomized controlled trials (RCTs) showed that 38–50% of patients with GERD and asthma controlled asthmatic problem by taking PPI for GERD.<sup>28,29</sup> The observational study from Pakistan evaluated the association between dental caries and gingivitis in 187 patients with reflux esophagitis from four hospitals and found that the patients with grade C or D reflux esophagitis had higher rate of severe dental caries, gingivitis, and complications.<sup>30</sup> Last, the symptom of chronic cough from extraesophageal GERD disappeared completely after laparoscopic Nissen fundoplication in half of the affected patients.<sup>31</sup> However,

extraesophageal symptoms have low sensitivity for GERD diagnosis.<sup>32</sup>

In addition, the 2015 guideline from the American Society for Gastrointestinal Endoscopy does not recommend performing EGD in patient with extraesophageal GERD who have no alarm features and response to PPI high dose (twice daily).<sup>33</sup> Thus, the committee suggest that patients with extraesophageal GERD without alarm features need to undergo complete history taking and physical examination to exclude other organic disease. A basic investigation (e.g. chest X-ray in patients with chronic cough) should be carried out when necessary. If after careful evaluation the results are negative, these patients may be diagnosed as extraesophageal GERD if the PPI test is responsive. Owing to imprecision and considerable bias, the level of evidence is low.

**Statement 3.2:** Careful cardiac evaluation is needed before diagnosing noncardiac chest pain (NCCP) from GERD.

Level of evidence: Moderate

Grade of recommendation: Conditional recommendation

#### Rationale

The committee suggests that complete physical examination and essential investigation, for instance electrocardiography, should be performed. If the diagnosis is still inconclusive, cardiologist consultation is recommended.

Although chest pain could be manifestation of various conditions, the majority of patients with NCCP have extraesophageal GERD. A study from Korea showed a high prevalence of GERD (48.2%) in NCCP patients.<sup>34</sup> Diagnosis of GERD in a PPI trial among patients presenting with NCCP had sensitivity and specificity of 80% and 74%, respectively.<sup>35</sup> Moreover, up to 70% of the patients with NCCP have normal esophageal manometry.<sup>36</sup> A meta-analysis of RCTs in 2015 comparing PPI and placebo in NCCP among GERD patients revealed that high-dose PPI can improve symptoms and benefit for diagnosing GERD.<sup>37</sup> However, the number of patients in this meta-analysis was not large enough to establish the treatment effect. Thus, the level of evidence is moderate.

**Clinical question 4:** Does PPI trial benefit GERD diagnosis?

**Statement 4:** Patients with typical reflux symptoms without alarm features can be diagnosed as GERD if they respond to a 2-week PPI trial.

Level of evidence: Very low

Grade of recommendation: Conditional recommendation

#### Rationale

A prospective observational study of patients with suspected GERD based on a questionnaire showed that half (54%) of 197 GERD patients responded to a 2-week PPI trial, whereas one-third (33%) of 99 patients without GERD also had symptom improvement after the PPI trial regimen.<sup>38</sup> Thus, a 2-week PPI trial provided 54% sensitivity, 65% specificity, 75% positive predictive value, and 41% NPV for GERD diagnosis. However, if focusing on only 97 patients with typical reflux symptoms, the sensitivity and positive predictive value increased to 71% and 84%, respectively.<sup>38</sup>

In addition, the guidelines for the diagnosis and management of GERD in 2013 suggested using a 2-week PPI trial for patients with typical reflux symptoms, whereby GERD could be diagnosed in those who had a positive trial.<sup>8</sup> The committee concluded that a 2-week PPI trial can be used as a diagnostic tool in patients with

typical reflux symptoms who have no alarm features to prevent unnecessary investigation and referral. Nevertheless, because the data are limited and contradictory, the level of evidence is classified as very low.

**Clinical question 5:** What is the appropriate next step in investigating refractory GERD patients?

**Statement 5:** Upper endoscopy is recommended for refractory GERD if patients fail to respond to PPI therapy optimization.

Level of evidence: Low

Grade of recommendation: Conditional recommendation

#### Rationale

In general, the chance of detecting endoscopic evidence of reflux esophagitis in refractory GERD patients is low because the prevalence of nonerosive reflux disease (NERD) is higher than that of erosive reflux disease.<sup>39</sup> Additionally, short-term PPI treatment can heal esophagitis in 72–83% of patients.<sup>40,41</sup> Although the prevalence of Barrett's esophagus and peptic stricture in Asia<sup>42,43</sup> is low,<sup>44</sup> other esophageal diseases that clinically might mimic GERD, for example, eosinophilic esophagitis, esophageal dysmotility (evidence of food retention or esophageal spasm), pill-induced esophagitis, or infection<sup>45</sup> can be detected by upper endoscopy. Furthermore, endoscopic findings can offer physicians the possibility to select PPI therapy or pH monitoring.<sup>45</sup>

However, the committee determined that this statement should be a conditional recommendation given that the endoscopic accessibility is limited in rural areas of Thailand. In other words, physicians can apply investigation and management appropriate to their facilities.

**Clinical question 6:** Does *Helicobacter pylori* testing and treatment benefit patients with GERD?

**Statement 6.1:** Screening and treatment of *H. pylori* infection are not generally recommended in GERD patients.

Level of evidence: High

Grade of recommendation: Conditional recommendation

**Statement 6.2:** In GERD patients who require long-term PPI treatment, *H. pylori* screening and treatment should be considered for the prevention of progression of gastric histopathology to corpus atrophy or intestinal metaplasia.

Level of evidence: Moderate

Grade of recommendation: Conditional recommendation

Please refer to the supporting information

**Clinical question 7:** Does esophageal biopsy benefit refractory GERD patients who have no esophageal injury proven by EGD?

**Statement 7:** We are against routinely random esophageal biopsy in refractory GERD patients who have no esophageal injury proven by EGD. Esophageal biopsy should be performed only in refractory GERD patients who have clinical or endoscopic findings suggestive of eosinophilic esophagitis.

Level of evidence: Low

Grade of recommendation: Conditional recommendation

Please refer to the supporting information

**Clinical question 8:** Do esophageal manometry and esophageal pH monitoring benefit PPI-refractory GERD patients when the EGD findings are negative?

**Statement 8:** Esophageal manometry and/or esophageal pH monitoring should be considered in PPI-refractory GERD patients when the result of EGD is negative.

Level of evidence: Moderate

Grade of recommendation: Conditional recommendation

### Rationale

For patients with GERD symptoms who have inadequate response to medical treatment and in whom upper endoscopic findings are unrevealing, 24-h pH monitoring can be used to quantify whether the patient has esophageal acid reflux<sup>46,47</sup> while 24-h multichannel intraluminal pH-impedance monitoring can distinguish acid and weak acid from nonacid refluxes, and identify whether a reflux component is liquid, gas, or mixed, as well as swallowing events.<sup>48,49</sup> Hence, further evaluations can provide more details regarding diagnosis in patients with PPI-refractory GERD, for example, functional heartburn and reflux hypersensitivity, as the tests evaluate the correlations between acid/nonacid reflux events and symptoms. Moreover, supragastric belching, a cause of PPI-refractory symptoms, also could be detected by these tests.<sup>49–51</sup>

High-resolution manometry is used to evaluate esophageal motility disorders that might mimic GERD, such as achalasia,<sup>16,51–54</sup> with sensitivity and specificity of 93–98% and 96–98% respectively.<sup>55</sup> Moreover, rumination episodes or supragastric belching can also be detected by high-resolution impedance manometry when employed in the postprandial setting.<sup>56</sup>

In conclusion, these esophageal tests (pH-impedance monitoring and/or high-resolution manometry) in addition to EGD, when used in PPI-refractory GERD patients, can redirect therapy toward alternative diagnoses or different symptom mechanisms, thus helping to trigger specific management and reduce unnecessary use of PPIs.<sup>46,57</sup>

**Clinical question 9:** Does lifestyle modification benefit patients with GERD?

**Statement 9.1:** Weight reduction is recommended for GERD patients who are overweight or have recent weight gain.

Level of evidence: Moderate

Grade of recommendation: Conditional recommendation

**Statement 9.2:** Cessation of tobacco smoking and alcohol consumption are recommended for GERD patients.

Level of evidence: Moderate

Grade of recommendation: Conditional recommendation

**Statement 9.3:** Restraint from food for 3 h before bedtime and consideration of head-of-bed elevation are recommended for GERD patients with nocturnal symptoms.

Level of evidence: Moderate

Grade of recommendation: Conditional recommendation

Please refer to the supporting information

**Clinical question 10:** Is PPI superior to other medications for the control of GERD symptoms?

**Statement 10:** Standard-dose PPI for 4–8 weeks has more efficacy for the control of symptoms of GERD than histamine type 2 receptor antagonists and antacids. PPI is recommended as first-line treatment for GERD.

Level of evidence: High

Grade of recommendation: Conditional recommendation

### Rationale

Proton pump inhibitors are considered to be the most effective medications for the control of GERD symptoms, owing to their potent acid suppression. These drugs are widely prescribed for both EE and NERD. The standard dose of PPI is recommended as initial treatment for GERD (omeprazole 20 mg/day, rabeprazole 20 mg/day, lansoprazole 30 mg/day, pantoprazole 40 mg/day, esomeprazole 40 mg/day, and dexlansoprazole 60 mg/day).<sup>58</sup>

Treatment of reflux symptoms with PPIs are more effective than histamine type 2 receptor antagonists (H2RAs) for both EE and NERD.<sup>59</sup> A meta-analysis by Zhang *et al.* showed an overall symptomatic relief rate of PPI against NERD of 51.4% (95% confidence interval [CI] 0.433–0.595,  $P < 0.01$ ).<sup>60</sup> PPIs also had more efficacy in achieving mucosal healing and decreasing the relapse rate in EE.<sup>40</sup> Another systematic review of seven RCTs by Sigterman *et al.* revealed that PPIs were more effective than H2RAs in controlling GERD symptoms as an empirical treatment (risk ratio [RR] = 0.66, 95% CI 0.60–0.73,  $P < 0.01$ ) and decreasing the frequency of heartburn symptoms in NERD (RR = 0.78, 95% CI 0.62–0.97,  $P = 0.03$ ).<sup>61</sup> PPI other than omeprazole (lansoprazole, rabeprazole, and pantoprazole) also have similar efficacy and are superior to H2RAs in terms of heartburn symptom control, mucosal healing, and decreased relapse rates of EE.<sup>62</sup>

Alginates act by displacing the postprandial acid pocket and can be used as an additional drug for the control of breakthrough reflux symptoms. A meta-analysis of 14 studies showed that alginates increased the odds of resolution of GERD symptoms when compared with placebo or antacids (odds ratio [OR] = 4.42, 95% CI 2.45–7.97,  $P < 0.01$ ) but was less effective than PPIs or H2RAs (OR = 0.58, 95% CI 0.27–1.22,  $P < 0.01$ ).<sup>63</sup> The recommended alginates dose of 10–20 mL, four times daily, may augment symptom control in comparison with PPI alone.<sup>64,65</sup>

**Clinical question 11:** Is high-dose PPI superior to standard-dose PPI for the control of symptoms in PPI-nonresponsive GERD patients?

**Statement 11:** Although PPIs twice daily show no significant difference in symptomatic relief of heartburn compared with PPIs once daily in clinical trials, increasing the dose of PPI before further investigations in PPI-nonresponsive GERD is beneficial in an inadequate acid control GERD patient.

Level of evidence: High

Grade of recommendation: Conditional recommendation

### Rationale

A meta-analysis by Zhang *et al.* that examined four RCTs aimed to investigate treatment efficacy of GERD with PPIs (esomeprazole, lansoprazole, omeprazole, pantoprazole, or rabeprazole) taken twice per day *versus* once per day in a short-term setting (from 1 to 12 weeks). Data regarding the relief of heartburn symptoms were combined, whereby the pooled results did not show a significant difference between the two groups (OR = 1.29, 95% CI 0.82–2.02,  $P = 0.27$ ).<sup>66</sup> However, we suggest increasing the dose of PPI to a double dose when the optimal standard dose cannot achieve a clinical response. This suggestion is based on GERD treatment recommendations of international societies.<sup>8,17</sup> The support for increasing the PPI dose comes from studies of esophageal pH monitoring, which revealed that high-dose PPI could better control acid suppression than low-dose PPI.<sup>67</sup>

Subgroups of patients with GERD-related NCCP, defined by abnormal acid exposure or EE revealed by endoscopic examination,<sup>68</sup> but not frequent heartburn and a high intensity of unusual sensation in the throat,<sup>69</sup> responded to PPIs twice a day. A higher dose of PPIs substantially increased cumulative patient satisfaction with heartburn-relief rate after 4 weeks of PPIs once a day from 61.5% (16 of 26 patients) at 4 weeks to 76.9% (20 of 26 patients) at 8 weeks.<sup>70</sup> Specifically, this study showed that if the patients had more frequent acid reflux episodes

(up to  $\geq 10$  episodes), this indicated a response to PPIs twice a day among patients who were not responsive to PPIs once a day.<sup>70</sup> The symptom index is also useful for predicting responsiveness to PPIs even for a standard dose.<sup>70</sup> Owing to the limitation in availability and accessibility of EGD in some areas of Thailand, the committee agreed to suggest increasing the dosage of PPI from once to twice per day if the patients were not responsive to the standard dose of PPI.

**Clinical question 12:** Is PPI-switching therapy superior to increased dosage of previous PPI for the control of symptoms in PPI-nonresponsive GERD patients?

**Statement 12:** Switching PPIs in patients with PPI-nonresponsive GERD was as effective as increasing the PPI dosage to twice a day for the control of heartburn symptoms.

Level of evidence: Moderate

Grade of recommendation: Conditional recommendation

#### Rationale

Only one RCT was found to demonstrate the effect of lansoprazole, 30 mg twice per day, compared with 40 mg esomeprazole for the control of persistent heartburn symptoms despite standard-dose PPI for 8 weeks, which showed equal effectiveness in symptom control.<sup>71</sup> Another clustered randomization trial conducted in Canada indicated that switching the PPI to esomeprazole would result in a mean 0.071 (95% CI 0.091–0.051,  $P < 0.0001$ ) gain in quality-adjusted life months compared with continuing with another PPI (other than esomeprazole and lansoprazole) or H2RA therapy.<sup>72</sup> Another small uncontrolled study from Japan also suggested that switching PPI would improve reflux symptom.<sup>73</sup>

**Clinical question 13.1:** Is PPI combined with prokinetics superior to PPI monotherapy for control of GERD symptoms in PPI-nonresponsive GERD patients?

**Statement 13.1:** Addition of short-term prokinetics to PPI therapy in PPI-nonresponsive GERD patients shows a tendency toward GERD symptom improvement.

Level of evidence: Moderate

Grade of recommendation: Conditional recommendation

**Clinical question 13.2:** Is combination of PPI with alginate superior to PPI monotherapy for the control of GERD symptoms in PPI-nonresponsive GERD patients?

**Statement 13.2:** There is limited evidence for or against the combination of PPI and alginate as an adjunctive treatment of non-responsive GERD.

Level of evidence: Moderate

Grade of recommendation: Conditional recommendation

**Clinical question 13.3:** Is PPI with neuromodulator combination superior to PPI monotherapy for the control of GERD symptoms in refractory GERD patients?

**Statement 13.3:** There is limited evidence for against the combination of PPIs and neuromodulators as an adjunctive treatment in nonresponsive GERD patients.

Level of evidence: Moderate

Grade of recommendation: Conditional recommendation

Please refer to the supporting information

**Clinical question 14:** Is PPI superior to placebo for the control of NCCP symptoms?

**Statement 14:** High-dose PPI increases symptom relief of GERD-related NCCP.

Level of evidence: Moderate

Grade of recommendation: Conditional recommendation

#### Rationale

Evidence from a randomized, prospective, double-blind trial of 36 patients with GERD-related NCCP showed that taking 20 mg of omeprazole twice per day led to a significant reduction in the proportion of days with chest pain ( $P = 0.006$ ) and severity of chest pain ( $P = 0.032$ ) when compared with placebo. Also, a greater number of patients in the omeprazole group (81%) reported improvement of overall symptoms, compared with just 6% in the placebo group ( $P = 0.001$ ).<sup>74</sup> Another prospective trial was carried out in patients with a longer than 2-week history of unexplained chest pain. Patients were randomized and followed after a 4-week regimen of 40 mg of esomeprazole or twice-daily placebo. More patients in the esomeprazole group experienced significant relief of chest pain compared with placebo (38.7% vs 25.5%,  $P = 0.018$ ).<sup>75</sup> The results of these two studies support treatment of NCCP with a high dose of PPI.

**Clinical question 15:** Is PPI effective in patients with extraesophageal symptoms of GERD?

**Statement 15:** Treatment with PPI showed promising benefits in established extraesophageal GERD symptoms, especially in patients who also had typical symptoms of GERD.

Level of evidence: Low

Grade of recommendation: Conditional recommendation

Please refer to the supporting information

**Clinical question 16:** Is there any role for combination treatment with PPI and other medications in patients with typical reflux symptoms and extraesophageal symptoms?

**Statement 16:** There is inadequate or limited supporting evidence for the use of other add-on medication such as prokinetics, baclofen, gabapentin, or alginate for established extraesophageal GERD patients who do not respond to PPI treatment.

Level of evidence: Low

Grade of recommendation: Conditional recommendation

Please refer to the supporting information

**Clinical question 17:** In mild GERD, is on-demand therapy better than maintenance therapy after complete response?

**Statement 17:** In GERD patients who had complete response to initial treatment, either step-down or on-demand therapy provide similar efficacy for symptoms control.

Level of evidence: Moderate

Grade of recommendation: Conditional recommendation

#### Rationale

There are recent systematic reviews and meta-analyses comparing on-demand therapy with continuous daily PPI as maintenance treatment. The first study by Khan *et al.*, included 10 RCTs and 4574 NERD/mild EE patients with a follow-up period of 6–7 months. The results showed that on-demand PPI was superior to daily PPI (pooled OR = 0.50, 95% CI 0.35–0.72,  $P = 0.0002$ ).<sup>76</sup> While a low-quality evidence reported by Boghossian *et al.*<sup>77</sup> revealed that on-demand PPI may increase the risk of poor symptom control compared with continuous PPI use with RR = 1.71 (95% CI 1.31–2.21) among NERD and mild EE patients from six RCTs. Further evidence to support the comparable efficacy of both interventions was presented in a multicenter randomized study from Europe and South Africa,<sup>78</sup> in which 82% and 86% of patients in on-demand and continuous therapy groups, respectively, were satisfied with the treatment in terms of controlling heartburn and



regurgitation. On the basis of the aforementioned data, we concluded that on-demand therapy had efficacy comparable with that of step-down or continuous therapy.

**Clinical question 18:** In moderate to severe GERD, is maintenance therapy better than on-demand therapy?

**Statement 18:** “Continuous PPI therapy is effective in GERD patients with severe erosive esophagitis, severe or frequent recurrence of symptoms.”

Level of evidence: Low

Grade of recommendation: Conditional recommendation

#### Rationale

Severe EE is defined by endoscopic findings of LA grades C and D. There is only one RCT<sup>79</sup> comparing daily PPI treatment with on-demand esomeprazole directly for maintenance of healed EE, in which 69% of the population had LA grades B to D. The results showed that daily PPI was better than on-demand therapy for endoscopic remission at 6 months (81% vs 58%,  $P < 0.0001$ ). Heartburn was also lower in the daily PPI treatment group than in the on-demand group, but overall symptomatic relapse was not different. A more recent employment of novel therapy with PCABs has been reported in a double-blind RCT for maintenance of healed EE by 20 and 10 mg of vonoprazan compared with 15 mg of lansoprazole, whereby the recurrence rate of EE at 24 weeks was 2% versus 5.1% versus 16.8%, respectively ( $P < 0.0001$ ).<sup>80</sup> A network meta-analysis also confirmed the efficacy of vonoprazan in the maintenance of healed EE for severe EE.<sup>81</sup> In terms of symptoms control, severity and frequency of GERD symptoms in the studies were evaluated by modified Likert scale or scoring questionnaires. Severe symptoms were usually defined as having incapacitating symptoms that interfered with daily activities,<sup>82,83</sup> although both severity and frequency of symptoms may not be associated with esophagitis findings.<sup>84</sup> As the natural history in NERD patients revealed that over 60% of them had frequent relapse with moderate to severe symptoms,<sup>85</sup> long-term treatment in this group of GERD patients is necessary. A randomized study showed that the continuous-treatment group had slightly higher symptomatic relief rates than the on-demand treatment group at 6 months (86.4% vs 74.6%,  $P = 0.065$ ) and had more overall satisfaction (visual analog scale 90 mm vs 83 mm,  $P = 0.026$ ).<sup>86</sup> Among patients with EE, heartburn was also lower in the daily PPI treatment group than in the on-demand group although symptomatic relapse was not different.<sup>79</sup>

Moreover, up to 75% of patients with NERD and 90% of patients with EE experienced symptomatic relapse within 6 months after refraining from medication.<sup>87,88</sup> A population-based study conducted in the United States since 2003 comprising GERD patients who required more than single-dose PPI revealed that almost 80% of patients did not report symptom recurrence during 6 months after step-down to single-dose PPI.<sup>89</sup> A systematic review of rebound acid hypersecretion in reflux patients also did not report signs or symptoms caused by acid rebound.<sup>90</sup>

**Clinical question 19:** In severe EE, is PCAB therapy better than PPI therapy?

**Statement 19:** PCAB is effective and noninferior to PPIs for healing and maintenance of healed EE. In addition, PCABs have a trend toward higher healing rates than PPIs in patients with severe EE.

Level of evidence: High

Grade of recommendation: Conditional recommendation

#### Rationale

Randomized controlled trials of more than 1500 patients with EE<sup>91–93</sup> and a network meta-analysis<sup>94</sup> have demonstrated that vonoprazan 20 mg was effective and noninferior to lansoprazole, 30 mg daily in healing EE at Week 8. EE healing rates at 2 and 4 weeks were slightly higher with 20-mg vonoprazan compared with 30-mg lansoprazole treatment.<sup>91</sup> In subgroup analyses of patients with severe EE (LA grades C to D) from two RCTs,<sup>91,93</sup> vonoprazan 20 mg daily is significantly more effective than lansoprazole, 30 mg daily for healing EE at Week 8. Both of these studies were conducted in an Asian population. Another RCT of 607 patients with endoscopically confirmed healed EE by vonoprazan, the rates of EE recurrence during the 24-week maintenance period were 16.8%, 5.1%, and 2.0% with lansoprazole 15 mg, vonoprazan 10 mg, and vonoprazan 20 mg, respectively ( $P < 0.0001$  for lansoprazole vs both doses of vonoprazan;  $P > 0.05$  between the two doses of vonoprazan).<sup>80</sup> In addition, a network meta-analysis of 22 RCTs reported that the efficacy of vonoprazan for maintenance treatment of healed EE was higher than that of some PPIs.<sup>81</sup> It should be noted that major RCTs comparing vonoprazan with lansoprazole for healing and maintenance of EE were predesigned statistically as noninferiority trials.<sup>80,91,93</sup>

**Clinical question 20:** In severe EE, are PPIs combined with other therapy better than PPIs alone?

**Statement 20:** In patients with EE, combination treatment of PPIs with other medications including prokinetics, rebamipide, and alginates, has been shown to be more effective than PPI alone in improving GERD symptoms. However, no convincing evidence that such combinations are better than PPI monotherapy for the healing of EE has been demonstrated.

Level of evidence: Moderate

Grade of recommendation: Conditional recommendation

**Clinical question 21:** Does long-term PPI use reduce the risk of esophageal cancer in patients with Barrett’s esophagus?

**Statement 21:** Long-term PPI use may reduce esophageal cancer risk in patients with Barrett’s esophagus. We recommend that patients be referred to a specialist.

Level of evidence: Low

Grade of recommendation: Conditional recommendation

Please refer to the supporting information

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## Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Data S1.** Supporting Information.