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Review

Thailand Dyspepsia Guidelines: 2018

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The management of dyspepsia in limited-resource areas has not been established. In 2017, key opinion leaders throughout Thailand gathered to review and evaluate the current clinical evidence regarding dyspepsia and to develop consensus statements, rationales, levels of evidence, and grades of recommendation for dyspepsia management in daily clinical practice based on the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach. This guideline is mainly focused on the following 4 topics: (1) evaluation of patients with dyspepsia, (2) management, (3) special issues (overlapping gastroesophageal reflux disease/irritable bowel syndrome and non-steroidal anti-inflammatory drug/aspirin use), and (4) long-term follow-up and management to provide guidance for physicians in Thailand and other limited-resource areas managing such patients.
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Key Words
Dyspepsia; Guideline; Thailand

Introduction

Dyspepsia is a common condition associated with gastrointestinal (GI) disease, with a global prevalence of at least 20%.[1] In Thailand, the prevalence of dyspepsia is 66%. Of those, 60-90% show no evidence of structural disease on endoscopy, which is known as functional dyspepsia (FD).[2] In addition, quality of life is significantly negatively impacted in dyspeptic patients in Asia.[3,4] The Thailand dyspepsia guideline has been developed to update the statement with essential practical points, rationales, levels of evidence, and grades of recommendations for the management of dyspepsia. The

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guideline is mainly for Thailand, but it could be generalized to other limited-resource countries all over the world. In this meeting, 22 key opinion leaders gathered from around the country to review and evaluate the current available evidence on dyspepsia. The meeting mainly focused on the following 4 issues: (1) evaluation of patients with dyspepsia, (2) management, (3) special issues (overlapping gastroesophageal reflux disease [GERD)/irritable bowel syndrome [IBS] and non-steroidal anti-inflammatory drugs [NSAIDs]/aspirin [ASA]), and (4) long-term follow-up and management.

Methods

At the beginning of the meeting, all members were divided into the following 6 working groups: (1) definition and epidemiology, (2) evaluation of patients with dyspepsia, (3) management, (4) special issues (overlapping GERD/IBS and NSAIDs/ASA), (5) long-term follow-up and management, and (6) cost-effectiveness. The working groups discussed and wrote preliminary clinical questions for each of the 6 areas during the first meeting. Current important clinical evidence and research were identified and analyzed by each working group. Statements were then submitted on the website in a specific template. The definition of each term/word was established by the first working group before voting. Then, all members voted and independently left comments on the website.

Later, the results of the online voting were discussed during a final face-to-face meeting in November 2017 in Bangkok to reach a consensus. The chairman and secretary of the first working group (definition and epidemiology) and the last working group (cost-effectiveness) explained the information and evidence related to their statements to all the voting members, but those statements were not chosen for further discussion. Consequently, 4 topics, namely, (1) evaluation of patients with dyspepsia, (2) management, (3) special issues (overlapping GERD/IBS and NSAIDs/ASA), and (4) long-term follow-up and management, were finally left for discussion in the final meeting. The level of evidence was determined by one member (R.P.) based on the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach (Table 1).[5] Consensus was achieved when 80% or more of the voting members indicated "strongly agree" or "agree." The strength of the recommendation was developed using the GRADE system (Fig. 1)[5] and defined as "recommend" only if 80% or more of the voting members indicated "strongly recommend." Otherwise, the strength of the recommendation for those statements was defined as "suggest" or "conditional recommendation."

Finally, there were 11 consensus statements written regarding the 4 topics (Table 2). All the statements and rationales were written by a secretary and proofread by the chairman of each working group. All final approved statements, rationales, levels of evidence, and grades of recommendation are summarized in this manuscript. An algorithm for the management of uninvestigated dyspepsia is also proposed in this guideline (Fig. 2).

Definition

In this guideline, "dyspepsia" refers to a heterogeneous group of symptoms in the upper abdomen and implies upper GI tract pathophysiology without alarm symptoms for at least 4 weeks (the majority of consensus members agreed that patients with dyspeptic symptom duration of "at least 4 weeks" should meet this guideline). Dyspepsia is often broadly defined as pain or discomfort centered in the upper abdomen, but it may include other symptoms, including epigastric pain or burning, sensation of fullness, early satiation, anorexia, belching, nausea and vomiting, upper abdominal bloating, and heartburn and regurgitation.[6] Of these symptoms, bloating has been reported as the most common manifestation in dyspeptic patients in Asian countries.[7]

Currently, only 4 symptoms (postprandial fullness, early satiation, epigastric pain, and epigastric burning) are considered specific to a gastroduodenal origin, although other symptoms may coexist with dyspepsia.[6] Thus, the symptoms and signs that are more specific to other organic diseases, such as esophageal, hepatobiliary or

Table 1. Level of Evidence by the Grading of Recommendations, Assessment, Development, and Evaluation System

GRADE ranking	Meaning
High quality	Further research is very unlikely to change our confidence in the effect estimate.
Moderate quality	Further research is likely to have an important impact on our confidence in the effect estimate and may change the estimate.
Low quality	Further research is very likely to have an important impact on our confidence in the effect estimate and is likely to change the estimate.
Very low quality	We are very uncertain about the estimate.

GRADE, the Grading of Recommendations, Assessment, Development, and Evaluation.

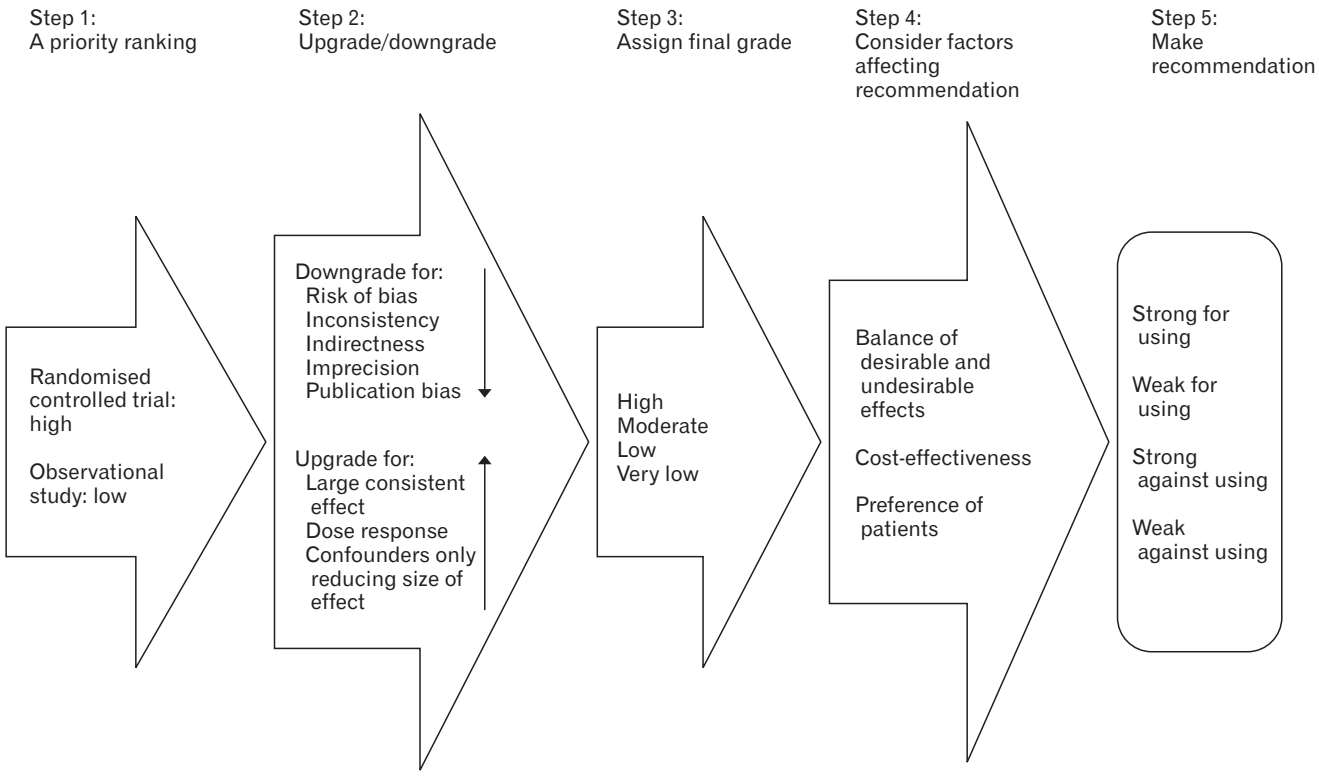

Figure 1. The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system.

large bowel diseases, should be excluded before making a diagnosis of "dyspepsia" according to this guideline. Overlap between dyspepsia, IBS, and GERD is possible.

"Uninvestigated dyspepsia (UD)" refers to dyspeptic symptoms in people who have not yet undergone specific diagnostic investigations. However, the preventable causes of dyspepsia, such as medications (eg, NSAIDs and ASA) and lifestyle (eg, stress and consuming a late dinner), must be excluded. A specific diagnosis that explains the dyspeptic symptoms but is made after the investigation is described as secondary dyspepsia, according to Rome IV criteria.[6]

"Functional dyspepsia" is when dyspeptic symptoms cannot be explained by a routine clinical evaluation, including endoscopy, and there is no evidence of *Helicobacter pylori* infection.[6,8] FD is divided into 2 subcategories: (1) Postprandial distress syndrome, which is characterized by symptoms such as postprandial fullness and early satiation that are related to meal. (2) Epigastric pain syndrome, which is characterized by symptoms such as epigastric pain and epigastric burning that are not related to meals.[6] Both syndromes are under the umbrella term of FD, and the treatment may differ, probably due to differences in the pathophysiology.[9,10]

Epidemiology

Dyspepsia is a common GI condition worldwide.[6] The prevalence of dyspepsia reported in a Thai population was approximately 66%.[2] The worldwide prevalence of UD varies from 7% to 34%,[6,7] with a pooled UD prevalence from 21 Southeast Asian studies of 21.6%.[7] The variation in UD prevalence seems to be related to the different definitions of UD used in individual surveys. Approximately 25% of dyspepsia cases have an underlying organic cause.[11] In Asian populations, the risk of malignancy associated with UD is approximately 1.3% (95% CI, 0.80-2.10).[12] Secondary dyspepsia was identified in 18% of UD patients after undergoing an endoscopy in Asian countries.[7] The global prevalence of FD is at least 70-80% of individuals with dyspepsia, as indicated by endoscopy-based studies.[9,13] In Thailand, approximately 60-90% of patients with dyspepsia are eventually diagnosed with FD.[2] The prevalence of FD appears to be generally higher in Western populations than Eastern populations, regardless of which iteration of the Rome criteria definition is used.[10,14] However, the prevalence of FD subtypes has not been extensively studied. A Korean study reported that 68.2% of patients with dyspepsia also experienced postprandial discomfort, and 46.4% experienced epigastric pain/soreness.[15]

Table 2. Summary and Strength of Recommendations

Topic 1: Evaluation of patients with dyspepsia
Statement 1: Esophagogastroduodenoscopy is indicated in dyspeptic patients who have one of the following: (1) Age of onset of 50 years or older (2) Alarm features (3) Symptoms are non-responsive to a trial of appropriate medical therapy. **Level of evidence: low** **Grade of recommendation: recommend**
Statement 2: In patients with dyspepsia, a rapid urease test and/or histopathology for *H.pylori* is in italics should be performed when endoscopy is indicated. **Level of evidence: moderate** **Grade of recommendation: recommend**
Topic 2: Management
Statement 3: Due to limited *H. pylori* testing resources in rural areas of Thailand, patients with uninvestigated dyspepsia without alarm symptoms should receive an empirical trial of PPIs for 4-8 weeks as a first-line therapy. **Level of evidence: moderate** **Grade of recommendation: suggest**
Statement 4: Prokinetic agents may be used as an adjunct therapy in patients with uninvestigated dyspepsia who fail to improve after empirical PPI therapy. **Level of evidence: very low** **Grade of recommendation: suggest**
Statement 5: *H. pylori* should be eradicated in all dyspeptic patients with *H. pylori* infection. **Level of evidence: high** **Grade of recommendation: recommend**
Statement 6: Prokinetic agents, tricyclic antidepressants and cytoprotective agents have been shown to improve symptoms in patients with FD after failure of PPI therapy. **Level of evidence: moderate** **Grade of recommendation: suggest**
Topic 3: Special issues (overlapping GERD/IBS and NSAIDs/ASA)
Statement 7: Overlapping GERD and FD should be managed with PPIs and/or prokinetic agents according to symptom subset. **Level of evidence: low** **Grade of recommendation: suggest**
Statement 8: Overlapping FD and IBS should be managed according to symptoms. **Level of evidence: very low** **Grade of recommendation: suggest**
Statement 9: Co-prescribing PPIs is the most effective strategy for reducing NSAID/ASA-induced dyspepsia, as well as NSAID/ASA-induced ulcer complications in high-risk patients. **Level of evidence: moderate** **Grade of recommendation: suggest**
Topic 4: Follow-up and long-term management
Statement 10: Patients with FD who respond to PPIs should be weaned off PPIs after achieving symptom relief within 6-12 months, while an appropriate lifestyle modification is mandatory. **Level of evidence: very low** **Grade of recommendation: suggest**
Statement 11: In patients with FD who do not respond to optimal treatment, the clinician should re-evaluate and consider further investigation. **Level of evidence: moderate** **Grade of recommendation: recommend**

H. pylori, *Helicobacter pylori*; PPI, proton pump inhibitor; FD, functional dyspepsia; GERD, gastroesophageal reflux disease; IBS, irritable bowel syndrome; NSAIDs, non-steroidal anti-inflammatory drugs; ASA, aspirin.

FD is a benign but chronic condition that often fluctuates and is sometimes recurrent.[9,16,17] It has a significant negative impact on the patient's quality of life as well as the health care system.[3,4] From a survey of 2000 rural populations in Malaysia, the quality of life score was significantly lower in dyspepsia patients compared to the healthy population.[4]

Evaluation of Patients With Dyspepsia

Statement 1: Esophagogastroduodenoscopy (EGD) is indicated in dyspeptic patients who have one of the following:

(1) Age of onset of 50 years or older

(2) Alarm features

(3) Symptoms are non-responsive to a trial of appropriate medi-

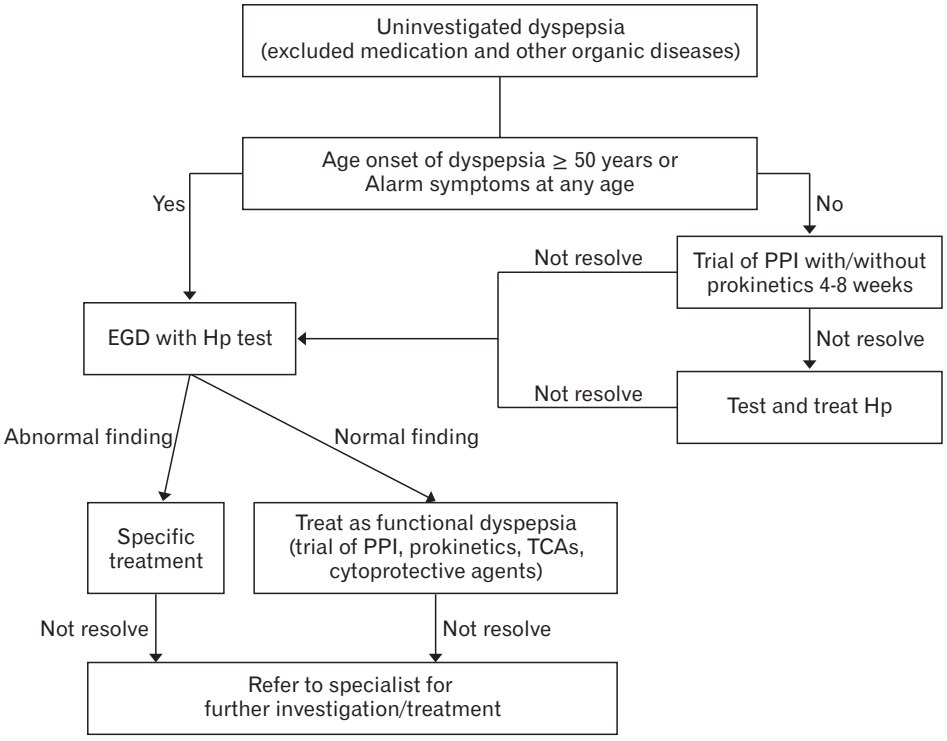

Figure 2. Algorithm for uninvestigated dyspepsia treatment. EGD, esophagogastroduodenoscopy; Hp, *Helicobacter pylori*; PPI, proton pump inhibitor; TCAs, tricyclic antidepressants.

cal therapy.

Level of evidence: low

Grade of recommendation: recommend

Consensus level: 90.5%

Rationale: The etiology of dyspepsia could be either an organic or a functional disease. In Thailand, age-specific incidence rates of gastric cancer are 5/100 000 people at age 40 years and increase abruptly to more than 10/100 000 people at age > 50 years.[18] Thus, the committee of this meeting agreed to decrease the previous age threshold for performing EGD in dyspeptic patients from an age of onset of older than 55 years to an age of onset of older than 50 years, as the evidence shows that the incidence of gastric cancer is significantly increased among individuals aged over the age of 50 years.

Dyspeptic patients with a high probability of malignant etiology, called "alarm features," should be appropriately investigated by EGD. These alarm features include evidence of upper GI bleeding, such as hematemesis, melena, maroon stool, or iron deficiency without other causes;[19] early satiety; unexplained weight loss (> 10% body weight); persistent vomiting due to an unknown cause (defined as vomiting > 10 times in 24 hours or vomiting after each meal); and family history of upper GI cancer in a first-degree relative, with each feature increasing the risk of upper GI malignancy 2-3 fold.[20,21] In addition, patients whose symptoms do not respond to a proton pump inhibitor (PPI) trial or those who are *H. pylori*-negative following a "test and treat" approach should proceed to EGD to identify the anatomical pathology or identify other diseases, such as FD.[20] This approach can reduce health anxiety in Asian patients.[22] However, other investigations in addition to EGD should be considered in patients on a case-by-case basis.

Due to the low cost-effectiveness, the 2017 American College of Gastroenterology (ACG) and the Canadian Association of Gastroenterology (CAG) guidelines on dyspepsia do not suggest the use of EGD to investigate alarm features in dyspeptic patients under the age of 60, as a means to exclude neoplasia.[21] However, the current committee agreed not to adopt their statement in this guideline. In fact, the expense of EGD in Thailand is not as costly as it is in North America; therefore, cost-effectiveness should not be the reason that EGD is not performed in patients who already have a risk of upper GI cancer.

Statement 2: In patients with dyspepsia, a rapid urease test and/or histopathology for *H. pylori* should be performed when endoscopy is indicated.

Level of evidence: moderate

Grade of recommendation: recommend

Consensus level: 100%

Rationale: The benefit of symptom relief from *H. pylori*

eradication was established for FD (relative risk [RR] = 1.23; 95% CI, 1.12-1.36; $P < 0.0001$),[23] with a number needed to treat (NNT) = 13, compared with placebo.[19] In addition, *H. pylori* infection has a strong association with the development of gastric adenocarcinoma.[24] It is reasonable to test for *H. pylori* in all patients with dyspepsia for whom EGD is indicated and treat the infected cases,[8,25] despite the controversy over its cost effectiveness compared with acid suppression therapy.[26]

A prospective study from Saudi Arabia, where the prevalence of *H. pylori* is high, showed that dyspeptic patients with normal mucosa had a 65% positive rate of *H. pylori* infection.[27] Another prospective study from Korea using standard endoscopy to predict the status of *H. pylori* infection in dyspeptic patients revealed that 9.4% of patients with normal vascular patterns have an *H. pylori* infection.[28] These results imply that endoscopic findings by standard endoscopy alone have limitations in predicting *H. pylori* infection status. Therefore, direct testing for *H. pylori*, including a rapid urease test and/or histology, should be considered. The rapid urease test is the most useful test for diagnosing *H. pylori* infection in routine endoscopy practice because it is rapid, inexpensive and easy to perform.[29] Histology is another biopsy-based test that provides higher accuracy than the rapid urease test,[29] but is more expensive and lacks standardization and availability.

Management

Statement 3: Due to the limited *H. pylori* testing resources in rural areas of Thailand, patients with uninvestigated dyspepsia without alarm symptoms should receive an empirical trial of PPIs for 4-8 weeks as a first-line therapy.

Level of evidence: moderate

Grade of recommendation: suggest

Consensus level: 91.4%

Rationale: The majority of patients with UD have an acid-mediated condition that should respond to acid suppression.[30] A meta-analysis from 4 randomized controlled trials (RCTs) showed that PPIs can achieve an estimated NNT of 5 in treating patients with UD, as the most frequent causes of UD include medication-induced gastritis and peptic ulcer, thus minimizing the need for more costly and invasive testing.[31] Additionally, approximately 60-90% of dyspeptic patients in Thailand are eventually diagnosed with FD after endoscopic evaluation;[2] thus, PPI trials should be initiated as a first-line treatment.

A meta-analysis of RCTs conducted in Western countries comparing "test and treat" and empirical PPI strategies revealed no difference in symptoms or treatment costs at the 12-month follow-up.[32] In addition, persistent dyspeptic symptoms, costs, and patient satisfaction were similar between the two strategies at 12 months after treatment in a Western population.[33] Nevertheless, the improvement in dyspeptic symptoms in Asian FD patients upon *H. pylori* eradication is 5-10% greater than in Western patients.[14] This may suggest superior cost effectiveness and patient satisfaction in Asian UD populations given an *H. pylori* "test and treat" strategy compared to Western populations. Currently, there is not robust support for this perspective due to the absence of cost effectiveness data for empirical PPI vs *H. pylori* "test and treat" in an Asian setting.

Importantly, neither non-invasive nor invasive *H. pylori* testing is available in rural areas of Thailand, and the Asian consensus report on FD in 2012[34] suggested the *H. pylori* "test and treat" strategy as first line treatment in all Asian dyspeptic patients only if socio-economic conditions allow. Consequently, in limited resource areas, an empirical trial of PPIs for 4-8 weeks should be applied first in patients under the age of 50 with dyspepsia without alarm symptoms. However, an *H. pylori* "test and treat" approach can be initially used in these patients if *H. pylori* testing is available.

Statement 4: Prokinetic agents may be used as an adjunct therapy in patients with uninvestigated dyspepsia who fail to improve after empirical PPI therapy.

Level of evidence: very low

Grade of recommendation: suggest

Consensus level: 85.7%

Rationale: Prokinetic agents can stimulate digestive tract motility via different mechanisms. They increase lower esophageal sphincter pressure, accelerate gastric emptying, and enhance antro-pyloric motility as well as fundic relaxation.[6] The possible relationship between dyspepsia and abnormal gastric emptying has provided the rationale for treatment trials of prokinetic agents.[35]

The efficacy of prokinetic agents has been focused on patients with FD, not UD. In the evidence used to develop the 2017 ACG/CAG guidelines on dyspepsia management, there was a trend showing superior efficacy of PPI over prokinetic agents without statistical significance (RR = 0.78; 95% CI, 0.60-1.02; $P = 0.06$).[21] A meta-analysis from Japan showed a statistically significant difference in the global reduction of symptoms in FD patients favoring prokinetic agents, with an odds ratio of 0.295 (95% CI, 0.208-0.382; $P < 0.001$), indicating a 30% higher probability of treatment response than placebo.[36] Based on the available evidence of the positive effects of prokinetic agents on dyspeptic symptom improvement and the availability in Thailand, the committee suggests offering prokinetic agents as an adjunct therapy for patients whose dyspeptic

symptoms do not respond to empirical PPI treatment, with a very low level of evidence. Importantly, patients should be advised of the side effects of prokinetic agents associated with long-term use.

Statement 5: *H. pylori* should be eradicated in all dyspeptic patients with *H. pylori* infection.

Level of evidence: high

Grade of recommendation: recommend

Consensus level: 100%

Rationale: *H. pylori* is a major human pathogen that causes chronic and progressive gastric mucosal damage and is etiologically related to peptic ulcer, gastric atrophy, and eventually gastric cancer.[8,24] It is also closely associated with dyspepsia.[37,38] Half of all patients with dyspepsia and *H. pylori* infection reported a greater than 50% symptom improvement after successful *H. pylori* eradication.[37] A symptom improvement evaluation should be performed at least 4 weeks after eradiation.[21] A meta-analysis comparing *H. pylori* eradication and placebo in patients with dyspepsia and *H. pylori* infection showed that *H. pylori* eradication was significantly superior to placebo in global symptom improvement (RR of remaining dyspeptic symptoms = 0.81; 95% CI, 0.70-0.94), with an NNT of 7 (95% CI, 5-14).[21]

Additionally, *H. pylori* eradication is able to stop the progression of mucosal damage, stabilize or reduce the risk of developing gastric cancer, improve gastric mucosal function, restore the normal mechanisms governing acid secretion, cure *H. pylori*-related peptic ulcer, reduce the risk of GI complications of NSAID therapy and prevent the future development of *H. pylori*-associated diseases.[24] *H. pylori*-positive individuals are also the major reservoir for transmission of the infection.[8,24] Therefore, this infection should be eradicated when it is found. However, the maximum benefit of eradication to prevent gastric adenocarcinoma is obtained in an individual if eradication is performed before the *H. pylori*-induced mucosal damage progresses beyond the atrophic stage.[8]

Statement 6: Prokinetic agents, tricyclic antidepressants (TCAs) and cytoprotective agents have been shown to improve symptoms in patients with FD after failure of PPI therapy.

Level of evidence: moderate

Grade of recommendation: suggest

Consensus level: 95.2%

Rationale: The management of patients with FD is challenging when the initial PPI therapy fails to improve their symptoms. The drug of choice in FD depends on its possible pathophysiology, including abnormal GI motility, visceral hypersensitivity, altered brain-gut function, psychosocial disturbance, and mild inflammation.[6,39,40]

A substantial proportion of patients with FD have disorders of gastric motility and/or poor accommodation;[41] thus, prokinetic agents have been developed that can accelerate gastric motion via various mechanisms, eg, non-selective 5-hydroxytryptamine 3 (5-HT_3) and 5-HT_4 receptor agonist (eg, metoclopramide), selective 5-HT_3 receptor antagonist (eg, active metabolite of mosapride), dopamine D2 receptor antagonist (eg, domperidone, itopride, and metoclopramide), and M1 and M2 muscarinic receptor antagonist (eg, acotiamide).[42] Based on the latest data from North America, prokinetic treatment significantly reduced the global symptoms of FD (RR of remaining dyspeptic symptoms = 0.92; 95% CI, 0.88-0.97), with an NNT of 12.5.[21] This information was supported by a previous meta-analysis in Japan in 2007.[36] Considering the adverse events related to metoclopramide and domperidone, the short-term use of these agents or the alternative use of other prokinetic agents could be recommended for the symptomatic relief of FD.[42]

Brain-gut axis dysfunction and abnormal central pain processing are the relevant mechanisms in FD.[43] The efficacy of TCAs has been established in patients with FD.[44] TCAs were introduced for a therapeutic trial in patients with FD whose symptoms did not improve after empirical PPI therapy.[21] Ford and colleagues reviewed 2795 relevant studies published through June 2015, including 13 RCTs that compared psychotropic drugs (n = 673) with placebo (n = 568) in adults with FD.[44] Overall, 57.7% of patients who received psychotropic drugs, compared with 71.7% of controls, reported persistent FD symptoms after treatment (RR = 0.78; 95% CI, 0.68-0.91; NNT = 6; 95% CI, 4-16).[44] The benefits were limited to TCAs such as amitriptyline[45,46] and did not extend to selective serotonin reuptake inhibitors.[45,47] Moreover, patients who received psychotropic drugs experienced more adverse events (RR = 1.28; 95% CI, 1.01-1.63) or an adverse event leading to withdrawal (RR = 1.76; 95% CI, 1.22-2.55) compared with placebo, with a number needed to harm of 21.[44]

Another sign of FD is mild inflammation, which may not be recognized by endoscopy but explains dyspeptic symptoms.[6,40] The efficacy of a cytoprotective agent, eg, rebamipide, was assessed in patients with persistent dyspeptic symptoms after receiving empirical PPI therapy[48] and successful *H. pylori* eradication.[49] Both studies concluded that rebamipide improved dyspeptic symptoms, mucosal inflammation on endoscopy, and histological features of chronic gastritis.[48,49] A 2017 systematic review and meta-analysis assessed 5 RCTs that investigated the efficacy of rebamipide in FD (one study from Khon Kaen, Thailand), and showed that patients

in the rebamipide group had a significantly better standard mean difference (SMD) in symptom scores than patients in controlled/comparator medication groups (SMD = −0.62; 95% CI, −1.16-−0.08; $P = 0.03$; $I^2 = 87\%$), but not in symptom improvement (RR = 1.01; 95% CI, 0.71-1.45; $P = 0.94$; $I^2 = 0\%$).[50] These data revealed the advantage of cytoprotective agents in dyspeptic symptom improvement in patients with FD.

Special Issues (Overlapping Gastroesophageal Reflux Disease/Irritable Bowel Syndrome and Non-steroidal Anti-inflammatory Drug/Aspirin)

Statement 7: Overlapping GERD and FD should be managed with PPIs and/or prokinetic agents according to symptom subset.

Level of evidence: low

Grade of recommendation: suggest

Consensus level: 100%

Rationale: The overlap between GERD and FD is common and is associated with greater symptom burden,[51] more physician consultations,[51] and poorer quality of life.[52,53] In Western populations, this condition affects up to half of patients with FD.[51,52] A general population study showed that an overlapping GERD/FD condition was associated with more frequent symptoms than either GERD or FD alone.[51] Upper GI symptoms, such as abdominal pain (90 vs 57 days/year) and postprandial distress (94 vs 53 days/year), occurred more frequently in the GERD/FD overlap group than in the dyspepsia-only group, as did lower GI symptoms, including diarrhea (71 vs 50 days/year) and constipation (94 vs 53 days/year) (all P-values < 0.05).[51] Higher somatization scores and insomnia were also associated with GERD/FD overlap compared with dyspepsia alone after adjustment for age, gender, and bowel symptoms.[52]

A common pathophysiology, such as visceral hypersensitivity, may explain the significant prevalence of this overlapping syndrome.[39] However, the therapeutic strategy for this condition has not been clearly established and has been limited to small studies. In Thailand, a 2-week trial of high-dose PPIs in 60 patients with overlapping non-erosive reflux disease and FD showed that PPI was effective for epigastric burning, acid regurgitation, heartburn, nausea, vomiting, and chest discomfort, but was not effective for early satiation, postprandial fullness, belching, or food regurgitation.[54] A randomized crossover study of tegaserod (5-HT_4 receptor agonist) in patients with overlapping FD and functional heartburn who had barostat-diagnosed visceral hypersensitivity showed a significant improvement in heartburn, regurgitation, early fullness, bloating, and gastric pain sensitivity after treatment, but not a global symptom improvement.[55] Therefore, the management of patients in this group should follow a systemic approach and consider other factors, such as multiple complaints of other GI symptoms or associated psychological factors.

Statement 8: Overlapping FD and IBS should be managed according to symptoms.

Level of evidence: very low

Grade of recommendation: suggest

Consensus level: 95%

Rationale: Several mechanisms have been proposed as common pathogenicities of overlapping dyspepsia/IBS,[56] which may guide the optimal treatment strategy.

Altered GI motility[57] and visceral hypersensitivity[58,59] have been shown to be the main pathophysiologies in patients with overlapping FD/IBS.

Very few RCTs have evaluated drugs targeting dyspepsia overlapping other GI disorders. Monnikes et al[60] studied 626 patients and found that PPIs significantly improved all symptoms (reflux, FD, and IBS) and that only reflux symptoms recurred after cessation of therapy. The mechanism of these effects is still unclear but is related to either a placebo effect or the real effect of an acid suppressant with a PPI in reducing visceral hypersensitivity, as the recurrence of reflux is quicker and more prominent than that of IBS. However, a clear therapeutic strategy has not been established due to the limited number of studies of overlapping dyspepsia/IBS.

Statement 9: Co-prescribing PPIs is the most effective strategy for reducing NSAID/ASA-induced dyspepsia, as well as NSAID/ASA-induced ulcer complications in high-risk patients.

Level of evidence: moderate

Grade of recommendation: suggest

Consensus level: 85%

Rationale: Dyspepsia is the most common complication arising from NSAID use, and it occurs in 15% to 30% of patients.[61] Dyspepsia has significant clinical and economic effects, as patients may discontinue necessary medications or require co-therapy for dyspepsia. Patients with a "high-risk" for upper GI complications from NSAIDs are patients with a history of previous complicated peptic ulcer (bleeding or perforation) or with 2 or more of the following: (1) elderly (> 65 years), (2) history of a previous uncomplicated peptic ulcer, (3) taking concurrent NSAIDs, or (4) taking concurrent ASA, steroids, or anticoagulants.[62] Patients with an *H. pylori* infection are defined as high-risk based on consensus among cardiologists.[63]

As the rates of GI complications vary among NSAID users, it is logical to use the NSAIDs with the lowest complication rates, such as ibuprofen, based on the assumption that such NSAIDs may also lead to a lower risk of developing dyspepsia.[64,65] However, selective cyclooxygenase-2 inhibitors (coxibs) have been shown to have lower rates of GI complications and dyspepsia than conventional NSAIDs.[64,65] Other strategies, including the use of coxibs or conventional NSAIDs, with co-prescription of an histamine H2 receptor antagonist (H2RA) or cytoprotective agents (eg, rebamipide), as well as PPIs, have been evaluated.

Available studies have mainly assessed the prevention and management of peptic ulcers and GI bleeding. For example, a Cochrane meta-analysis of 40 RCTs demonstrated that PPIs, misoprostol and double-dose H2RAs are effective in preventing chronic NSAID-related endoscopic peptic ulcers, and these agents are also likely to reduce NSAID-induced dyspepsia.[66] A meta-analysis comparing the rates of dyspepsia for conventional NSAIDs plus PPI vs coxibs alone in high-risk patients with arthritis showed that conventional NSAIDs plus PPI provided a greater risk reduction for dyspepsia than coxibs.[67] The use of H2RA has also shown some benefit, albeit a lower benefit than newer PPIs, with a 26% reduction in dyspeptic symptoms with H2RA versus a 6% reduction with placebo in patients taking NSAIDs, irrespective of underlying peptic ulcer disease.[68] Rebamipide has been shown to be as effective as misoprostol in the prevention of ulcer complications in long-term NSAID users, and it may be more effective in the reduction of NSAID-induced dyspeptic and lower GI symptoms.[69]

An RCT studying the efficacy of a 26-week co-administration of esomeprazole 20 mg/day compared with placebo and low-dose aspirin in patients > 60 years of age without *H. pylori* infection revealed that PPI reduced the occurrence of peptic ulcers (1.4% vs 4.9%, $P = 0.001$) and the cumulative proportion of patients with erosive esophagitis (4.4% vs 18.3%, $P < 0.0001$).[70] A recent RCT comparing 6 months of combination drugs (enteric-coated aspirin 325 mg and immediate-release omeprazole 40 mg) with aspirin alone in patients with a high risk of both cardiovascular and GI events demonstrated that both dyspepsia and esophagitis occurred less frequently in patients receiving combination therapy.[71] Furthermore, an 18-month follow-up RCT comparing a standard dose of a PPI plus naproxen 500 mg twice daily and a standard dose of a PPI plus celecoxib 100 mg twice daily in patients with previous peptic ulcer bleeding who required concomitant low-dose aspirin revealed that recurrent peptic ulcer bleeding was significantly lower in patients taking celecoxib plus PPI than in patients taking naproxen plus PPI, in high-risk patients (5.6% vs 12.5%, $P = 0.008$).[72]

Follow-up and Long-term Management

Statement 10: Patients with FD who respond to PPIs should be weaned off PPIs after achieving symptom relief within 6-12 months, while an appropriate lifestyle modification is mandatory.

Level of evidence: very low

Grade of recommendation: suggest

Consensus level: 94.7%

Rationale: According to the Rome IV criteria, it is recommended to continue PPIs and/or prokinetics as a long-term treatment when FD patients have achieved adequate relief from EPS and/or PDS.[6] In contrast, if the symptoms are not improved, especially within 4-8 weeks,[42] all agents should be discontinued, and other treatments should be identified.[6] However, no precise duration of treatment was mentioned in the Rome IV criteria.[6] In the previous review by the same world authorities group (Rome III), they suggested maintaining PPIs and/or prokinetic agents combined with lifestyle modification and re-starting during periods of symptom exacerbation.[73] Again, they did not propose a duration for these medications.[73] Recently, the 2017 ACG/CAG clinical practice guideline on dyspepsia management recommended stopping PPIs every 6-12 months to avoid PPI complications.[21] In practical terms, the physician should inform patients with chronic FD symptoms about the long-term adverse events of each medication and advise them to adjust the medications with the lowest dose and shortest duration for controlling dyspeptic symptoms. However, if the symptoms are not improved with these agents, patients should be advised to meet the physician for re-evaluation and appropriate further treatment.[2]

Statement 11: In patients with FD who do not respond to optimal treatment, the clinician should re-evaluate and consider further investigation.

Level of evidence: moderate

Grade of recommendation: recommend

Consensus level: 100%

Rationale: FD is a chronic and fluctuating disorder, but it has a very good prognosis.[16,17] In patients whose symptoms do not respond to standard medical therapy, the protocol should be to reconsider and re-evaluate. Clinical re-evaluation is mandatory. Overlap with other functional GI disorders and psychological comorbidities should be addressed and treated. The yield of repeat upper endoscopies in FD patients within 3 years is substantially low because all findings are acid-related disorders without malignancy.[74,75] Thus, repeat EGD could be considered if the procedure has

not been performed within the past 3 years. Ultrasonography of the upper abdomen should be performed if the patient has severe, intermittent episodes of pain or is suspected to have biliary colic. Gastric emptying time testing could be considered if available during physiological testing,[76] but it is mainly conducted in university hospitals and used for research purposes in Thailand. Serologic testing for celiac disease is not recommended due to a very low prevalence in Thailand.

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