Asian Consensus Report on Functional Dyspepsia

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Abstract

Background and Aims

Environmental factors such as food, lifestyle and prevalence of *Helicobacter pylori* infection are widely different in Asian countries compared to the West, and physiological functions and genetic factors of Asians may also be different from those of Westerners. Establishing an Asian consensus for functional dyspepsia is crucial in order to attract attention to such data from Asian countries, to articulate the experience and views of Asian experts, and to provide a relevant guide on management of functional dyspepsia for primary care physicians working in Asia.

Methods

Consensus team members were selected from Asian experts and consensus development was carried out by using a modified Delphi method. Consensus teams collected published papers on functional dyspepsia especially from Asia and developed candidate consensus statements based on the generated clinical questions. At the first face-to-face meeting, each statement was reviewed and e-mail voting was done twice. At the second face-to-face meeting, final voting on each statement was done using keypad voting system. A grade of evidence and a strength of recommendation were applied to each statement according to the method of the GRADE Working Group.

Results

Twenty-nine consensus statements were finalized, including seven for definition and diagnosis, five for epidemiology, nine for pathophysiology, and eight for management. Algorithms for diagnosis and management of functional dyspepsia were added.

Conclusions

This consensus developed by Asian experts shows distinctive features of functional dyspepsia in Asia and will provide a guide to the diagnosis and management of functional dyspepsia for Asian primary care physicians.

Introduction

Dyspepsia is one of the most common disorders in medicine, with dyspeptic patients seen on a daily basis not only by gastroenterologists but also by physicians in a variety of other fields. However, organic causes are found in only a minority of such patients. Functional dyspepsia (FD) is defined as a condition in which upper abdominal symptoms occur in the absence of organic disease that explains them. There are many FD patients in Asian as well as Western countries. The scientific investigation of the pathophysiology of FD began only recently and its first definition was developed in 1988.[1] Since then, many of the ideas on this condition have been derived from studies conducted in Western societies, despite the large number of FD patients in Asian populations and much important research from Asian countries.

Accordingly, the establishment of an Asian consensus for FD is crucial in order to attract attention to such data from Asian countries, to articulate the experience and views of Asian experts, and to provide a relevant guide to the management of this disease for primary care physicians working in Asia. In particular, environmental factors such as food, lifestyle and prevalence of *Helicobacter pylori* infection are widely different in Asian countries compared to the West, and physiological functions and genetic factors of Asians may also be different from those of Westerners. Therefore, the

Asian perspective should be useful for further understanding the pathogenesis of FD.

The understanding of FD is progressing and will evolve over time. We have summarized the current Asian perspective on FD in this consensus report, which will be revised as our understanding of FD grows.

Methods

The Asian Pacific Association of Gastroenterology (APAGE) and the Asian Neurogastroenterology and Motility Association (ANMA) agreed to jointly generate an Asian consensus report on FD and organized 4 teams for that purpose: Team 1, definition and diagnosis; Team 2, epidemiology; Team 3, pathophysiology; and Team 4, management. Twenty-two consensus team members were recruited from Asian countries on the basis of each member's scientific activities and published papers on FD.

The consensus development process was carried out by using a modified Delphi method.[2] Consensus team members started their job in late June 2009 by collecting original papers on FD from Asian countries until the end of August 2009 through available global and domestic online literature searching systems. Papers in English and other languages that were not available online were searched manually. Thereafter the remaining important original and review papers not only from Asia but also from rest of the world were also collected and added. When a new paper was published during the consensus process, it was also included. After thorough reviewing the literature, each team generated approximately 10 consensus statements through intra- and inter-team e-mail discussions, resulting in a total of 37 candidate consensus statements.

On September 19, 2010, the first Asian FD consensus meeting was held in Kuala Lumpur, Malaysia. At the meeting, each candidate statement was discussed in depth, and afterward, the statements were reviewed again and amended by the 4 teams, taking the discussions held at the first consensus meeting into consideration. At this point, 34 consensus statements had been developed.

The first e-mail voting on the consensus statements was done by all of the consensus members on October 26, 2010. Each member was asked to choose one of the following 6 levels of agreement on each statement (Table 1): (a) accept completely, (b) accept with minor reservation, (c) accept with major reservation, (d) reject with major reservation, (e) reject with minor reservation, and (f) reject completely. Consensus members were also asked to add comments on each statement, if any. When the proportion of members who voted (a) or (b) was 80% or higher, the statement was regarded as acceptable and a consensus was considered to have been reached. In the first e-mail vote, 25 of the 34 statements (73.5%) were acceptable and the remaining 9 statements (26.5%) failed to reach the consensus level.

After extensive discussions and subsequent revision of the consensus statements, the second e-mail voting was done on 35 statements on January 11, 2011. From this voting, 30 statements (85.7%) were acceptable while 5 statements (14.3%) were

unacceptable. Each statement was reviewed and amended again by each team, and a total of 32 consensus statements were developed for final voting.

On March 3, 2011, the second Asian FD consensus meeting was held in Beijing, China. At the plenary meeting, voting on each statement was done by using a keypad voting system. After each vote, a discussion was held, and if necessary, the statement was revised and voted on again until a consensus was reached. At the conclusion of this process, 29 consensus statements (seven on definition and diagnosis, five on epidemiology, nine on pathophysiology, and eight on management) had been finalized. A grade of evidence and a strength of recommendation were applied to each statement according to the GRADE Working Group (Table 1).[3] Algorithms for diagnosis (Fig. 1) and management (Fig. 2) of FD were made after the statements had been finalized.

Consensus Statements

Definition and diagnosis

Statement 1. Dyspepsia refers to a symptom or set of symptoms that is (are) considered to originate from the gastroduodenal region. The dyspeptic symptoms are epigastric pain, epigastric burning, postprandial fullness, early satiation, and others, including bloating in the upper abdomen, nausea, vomiting, and belching.

Grade of evidence: not applicable.

Level of agreement: a: 89.5%; b: 5.3%; c: 5.3%; d: 0%; e: 0%; f: 0%.

For this statement, the consensus members decided to follow the concept of the Rome III Committee that dyspepsia is a symptom or a group of symptoms that is (are) considered to originate from the gastroduodenal region.[4]

However, the consensus members agreed to include upper abdominal bloating which is a common FD symptom. Although there are limited data on the prevalence of upper abdominal bloating in FD in Asia, most of the consensus members felt that this symptom is very common in Asian dyspeptic patients. It was reported that bloating was present in about half of the dyspeptic patients in the United States[5,6] and was most

common in patients with dysmotility-like dyspepsia.[5] Studies in Korea and Japan demonstrated that postprandial distress syndrome (dysmotility-like dyspepsia) was present in 69.9% and 81.3% of patients with dyspepsia,[7] respectively. The overlapping of FD with other gastrointestinal (GI) motility disorders is common in Asia. It was reported that about one fourth of FD patients in China had overlapping irritable bowel syndrome (IBS).[8]

Statement 2. Functional dyspepsia is a condition characterized by chronic dyspeptic symptoms in the absence of organic, systemic or metabolic condition(s) that is (are) likely to explain the symptoms. (See Fig. 1)

Grade of evidence: not applicable.

Level of agreement: a: 89.5%; b: 10.5%; c: 0%; d: 0%; e: 0%; f: 0%.

The consensus members agreed that chronic dyspeptic symptoms could be continuous, intermittent or recurrent. However, symptom duration of 6 months or longer was considered too long to make a diagnosis of FD in Asia. A study in Japan suggested that most patients with dyspeptic symptoms present to their doctors within 6 months after the first appearance of their symptoms.[7] Twenty-six percent of the consensus members felt that in clinical practice a symptom duration of one month is enough to

consider dyspeptic symptoms as being chronic, whereas 68% agreed with a duration of 3 months and only 5% agreed with the 6-month period as in the Rome III criteria (Fig. 1). However, most of the consensus members agreed that for research purposes, diagnosis of FD in Asia could follow the Rome III diagnostic criteria for FD.

Many organic, systemic or metabolic conditions such as peptic ulcer diseases, cancers of the GI and hepatobiliary tract,[9,10] parasitic infestations,[11-14] chronic pancreatic diseases,[15] hyper- and hypothyroidisms,[16] chronic renal failures,[17] and electrolyte imbalances, as well as medications, can produce symptoms similar to FD and should be considered before making a diagnosis of FD.

Statement 3. Diagnosis of functional dyspepsia and functional dyspepsia subgroups based on the Rome III criteria needs validation in Asia.

Grade of evidence: low.

Level of agreement: a: 100%; b: 0%; c: 0%; d: 0%; e: 0%; f: 0%.

All consensus members agreed with this statement. Since Asian countries have large differences in culture and language, the interpretation of GI symptoms is likely to be different from country to country. Unfortunately, there are no cross-ethnic or cross-cultural studies to address this thesis currently.

Statement 4. A diagnosis of functional dyspepsia can be considered on the basis of clinical symptoms and upper gastrointestinal endoscopy results. (See Fig. 1)

Grade of evidence: moderate.

Level of agreement: a: 78.9%; b: 15.8%; c: 5.3%; d: 0%; e: 0%; f: 0%.

Most of the consensus members agreed that for most patients with dyspeptic symptoms in Asia the clinical symptoms and upper GI endoscopic results are sufficient to consider a diagnosis of FD. However, several studies in Asia also included upper abdominal ultrasound as an important investigative tool for diagnosis of FD.[18,19] Some patients with clinical features that cannot be explained by endoscopic findings may need further diagnostic investigations such as stool examination for parasites and occult blood, if clinically indicated (Fig. 1). For a diagnosis of FD, the upper GI endoscopic results should include no evidence of any diseases and conditions that can explain the dyspeptic symptoms. The presence of *H. pylori* infection in the absence of positive endoscopic findings does not exclude a diagnosis of FD presently.

Statement 5. Dyspepsia patients with alarm features should be investigated before the diagnosis of functional dyspepsia is accepted. (See Fig. 1)

Grade of evidence: high.

Level of agreement: a: 94.7%; b: 5.3%; c: 0%; d: 0%; e: 0%; f: 0%.

Although several studies suggested that alarm features have a low positive predictive value for the diagnosis of organic causes in patients with dyspepsia,[20] all of the consensus members agreed that if patients have any alarm features they should be investigated (Fig. 1). The alarm features are as follows: unintended weight loss; progressive dysphagia; recurrent or persistent vomiting; evidence of GI bleeding; anemia; fever; family history of gastric cancer; and new onset dyspepsia in a patient over 40 years of age in a population with high prevalence of upper GI malignancy, or over 45 or 50 years in a population with intermediate or low prevalence, respectively. (See under Statement 8 for further discussion.)

According to a recent review on the prevalence of gastric cancer in Asian countries,[21] China, Korea and Japan are high-risk countries; Hong Kong, Malaysia, Singapore, Taiwan and Vietnam are intermediate-risk countries; and Bangladesh, India and Thailand are low-risk countries. It has been reported in Japan that most patients with early gastric cancer are asymptomatic and lack alarm features.[10] Therefore, for early detection of gastric cancer in countries with high gastric cancer prevalence,

doctors should follow their national gastric cancer screening guidelines instead of this dyspepsia consensus statement.

Statement 6. Other useful investigations for dyspepsia include complete blood cell count and blood biochemistry tests. Patients with dyspepsia should be tested for *Helicobacter pylori* infection. Stool examination for parasites in areas with high prevalence of infestations and fecal blood testing are also useful. Upper abdominal ultrasound or CT scan may be employed if indicated clinically. (See Fig. 1)

Grade of evidence: moderate.

Level of agreement: a: 52.6%; b: 36.8%; c: 10.5%; d: 0%; e: 0%; f: 0%.

Most consensus members agreed that, if clinically indicated, complete blood count and blood biochemistry tests including tests for creatinine,[17] electrolytes, sugar, thyroid function[16] and liver function are useful for identifying underlying causes that may produce dyspeptic symptoms (Fig. 1). Although *H. pylori* testing is not used for diagnosis of FD, it is useful for the management of FD patients. Role of *H. pylori* is discussed under Statement 18. In areas with high prevalence of parasitic infestations, a stool exam for parasites is useful for identification of parasitic infestations such as ascariasis,[14] fascioliasis,[11] giardia lamblia[12] and opisthorchiasis[13] that can cause dyspeptic symptoms. Upper abdominal ultrasound or CT scan can be employed if

clinically indicated, especially in areas with high prevalence of liver cancers that can present with dyspeptic symptoms.[10]

Statement 7. Gastric sensorimotor function tests including gastric emptying or accommodation studies may be useful in some subgroups of patients but are not recommended as routine clinical tests.

Grade of evidence: high.

Level of agreement: a: 84.2%; b: 10.5%; c: 5.3%; d: 0%; e: 0%; f: 0%.

Gastric function tests including gastric emptying test, electrogastrography, water load test, gastric accommodation test and gastric sensation test play controversial roles in the diagnosis and management of FD.[22] These tests are poorly associated with dyspeptic symptoms and cannot predict a response to medical therapy in FD. Therefore, these tests should be reserved only for clinical research studies and evaluation in some specific subgroups of dyspeptic patients, such as patients with diabetic gastroparesis or generalized GI disorders.

Epidemiology

Statement 8. In Asian populations, the majority of patients with uninvestigated dyspepsia without alarm features have functional dyspepsia.

Grade of evidence: moderate.

Level of agreement: a: 68.4%; b: 21.1%; c: 10.5%; d: 0%; e: 0%; f: 0%.

In most studies from Asia, FD was diagnosed in most patients with uninvestigated dyspepsia (UD) after upper GI endoscopy.[23] In a Chinese study of 782 patients with UD, 69% turned out to have FD and the remaining 31% had organic causes.[24] In a multi-center Asian study of 1115 patients with UD (Rome II criteria) from 9 countries (China, Hong Kong, Indonesia, Korea, Malaysia, Singapore, Taiwan, Thailand, and Vietnam), 43% turned out to have FD after investigations.[25] In a Korean study of 476 patients with uninvestigated GI symptoms, 70% had functional GI disorders according to the Rome II criteria and 37% had FD.[26] In a Malaysian study of 210 young patients with UD, 62% were diagnosed with FD.[27] In a Singaporean study, of 988 of 5066 patients with UD had organic causes and the remaining 79.5% had FD.[28]

The cut-off age for considering a feature to be an alarm feature may vary in different populations based on the local epidemiological pattern of gastric cancer. In a

Japanese study that considered 50 years as the cut-off age, frequency of FD was found

to be lower among persons older than 50 years.[29] In another study from Japan, of 1730

gastric cancer patients, 27 were less than 34 years old.[30] A study from India showed that

patients with gastric cancer were older than patients with non-ulcer dyspepsia (53 ± 12

years vs. 43 ± 13 years).[31] These data might suggest that the cut-off age for considering

endoscopic examination may vary by geographical area, though most believe that it

should be 45 years of age.

Statement 9. A portion of Asian patients with functional dyspepsia has overlapping irritable bowel syndrome.

Grade of evidence: moderate.

Level of agreement: a: 100.0%; b: 0%; c: 0%; d: 0%; e: 0%; f: 0%.

In Asian patients, there is a significant overlap between FD and IBS. In a Chinese

study using the Rome III criteria, 24.8% of FD patients had overlapping IBS.[8] In a study

from India, dyspepsia-IBS overlap (dyspepsia was defined as abdominal pain or

discomfort centered in the upper abdomen and IBS by Manning's criteria) was found in

14.2% of the FD subjects.[32] Another Indian multi-center study demonstrated a high

frequency (90%) of upper abdominal pain or discomfort in IBS patients, although the

diagnosis in that study was based on the clinicians' assessment rather than on the Rome criteria.[33] In a Japanese study, the overlap of FD and IBS was found to be 3.5% of the patients with FD.[34] In a study from Hong Kong using the Rome I criteria, overlapping IBS was found to be 16.9% of the subjects with dyspepsia.[35] In a Japanese study using the Rome II criteria for the diagnosis of functional GI disorders, 181 medical students were recruited, and the overlap of IBS was found to be 66.7% of UD subjects.[36] In a Korean study of 476 patients with functional GI disorders according to the Rome II criteria, the overlap of IBS was found in 20.8% of FD patients.[26] In these studies, overlap of FD and IBS showed wide variation that might be due to diagnostic criteria, study populations, sociocultural issues, or symptom reporting by the patients.

Statement 10. Patients with functional dyspepsia may have overlap with gastroesophageal reflux disease.

Grade of evidence: moderate.

Level of agreement: a: 84.2%; b: 15.8%; c: 0%; d: 0%; e: 0%; f: 0%.

Overlap of FD and gastroesophageal reflux disease (GERD) is common in different Asian populations.[23] A study from Turkey showed overlap of GERD to be 29.4% of subjects with symptoms of dyspepsia,[37] and a study from Korea showed such overlap to

be 24.1% of FD subjects.[38] In both of those studies, GERD was diagnosed by questionnaire and not by 24-hour pH-impedance monitoring, which is currently the gold standard for diagnosis of GERD. Heartburn, which is the major symptom of GERD, may be influenced by the type of reporting by the patients because of sociocultural issues and lack of appropriate terminology in some Asian languages.[39]

Statement 11. Quality of life is impaired in patients with functional dyspepsia.

Grade of evidence: moderate.

Level of agreement: a: 84.2%; b: 15.8%; c: 0%; d: 0%; e: 0%; f: 0%.

Quality of life (QOL) is not good in patients with FD although it is not a fatal disease. The impairment of QOL in FD patients may be associated with significant burden on society due to work absenteeism, reduced productivity, and use of health care resources.[40,41] Data on QOL of patients with FD from Asia are scanty. However, in a Korean study of 1417 subjects, the frequency of dyspepsia was found to be 11.7% according to the Rome III criteria. The Korean version of SF-36 was used to evaluate health-related QOL, and in patients with dyspepsia, the scores were worse for all 8 domains.[42,43] Two studies from Malaysia by the same working team, one on a rural population and other on an urban population, showed using the EuroQOL (EQ-5D)

instrument that subjects with dyspepsia (Rome II and III criteria) had lower

health-related QOL.[44-46]

Statement 12. Psychological co-morbidity and socioeconomic factors may determine consultation behavior among patients with functional dyspepsia.

Grade of evidence: moderate.

Level of agreement: a: 100.0%; b: 0%; c: 0%; d: 0%; e: 0%; f: 0%.

Psychological illness is often associated with FD. In a Chinese study, psychological

co-morbidity was assessed by the Hamilton Rating Scale for Depression (HRSD) and

the Hamilton Anxiety Scale (HAS) in patients with FD and in healthy subjects before

and after treatment for this disease.[47] The data revealed a significant difference in

HRSD and HAS scores between the FD patients and healthy subjects. Also, treatment

with anti-depressant for 8 weeks resulted in improvement in scores. In a prospective,

cross-sectional Malaysian study of 839 patients with dyspepsia, there were 472 patients

with FD and 367 patients with organic causes.[48] This study showed that anxiety was

associated with both groups and that health-related QOL was lower in the patients with

FD than in the patients with organic dyspepsia. Psychological factors associated with

FD may influence consultation behavior in patients with FD. A population-based study

from Hong Kong revealed that anxiety was associated with medical consultation and sick leave among patients with dyspepsia.[35] The study showed that the degree of anxiety was an independent factor associated with health care-seeking behavior in dyspeptic patients. However, bloating and incomplete evacuation were found to be more important determinants of consultation behavior than psychological factors in a recent review of the epidemiology of IBS, which is another common functional bowel disease that may have overlapping dyspeptic symptoms.[49] More studies on this issue are needed.

Pathophysiology

Statement 13. Pathogenesis of functional dyspepsia is multifactorial.

Grade of evidence: high.

Level of agreement: a: 100.0%; b: 0%; c: 0%; d: 0%; e: 0%; f: 0%.

Many pathogenic factors have been proposed for FD, including motility abnormalities such as delayed gastric emptying, impaired gastric accommodation and hypersensitivity to gastric distension; psychological factors; excessive gastric acid secretion; *H. pylori*; genetics; environment in childhood and/or adolescence; diet; lifestyle; and prior GI infection.[50-52] The major mechanism thought to induce FD symptoms includes impaired accommodation, delayed gastric emptying, and visceral hypersensitivity, as well as other complicating factors.[51,53] Pharmacological correction of abnormal gastric motility and visceral hypersensitivity has been considered as a valid therapeutic approach in FD; however, changes in motor function and symptomatic outcomes are poorly correlated.[54]

Current evidence suggests that FD is a heterogeneous disorder in which different pathophysiological disturbances are associated with different symptom profiles. Progress

in understanding the underlying pathogenetic mechanisms should lead to better targeting of treatment in FD patients.[50]

Statement 14. Disturbed gastroduodenal motility is one of the pathophysiologic mechanisms in functional dyspepsia.

Grade of evidence: high.

Level of agreement: a: 100.0%; b: 0%; c: 0%; d: 0%; e: 0%; f: 0%.

Disturbed gastroduodenal motility is considered to be one of the major pathophysiologic mechanisms in FD.[4,51] Abnormal gastric motility has been analyzed from different aspects by various measures, and differences in findings between health and diseases have been characterized.

We intuitively recognize that delayed gastric emptying may be related to dyspeptic symptoms, especially feelings of retention of ingested food after meal, which can be abdominal distension, bloating or fullness. There are many reports demonstrating delayed gastric emptying in patients with FD from both Western[55,56] and Asian[57-63] countries, and about 40% of FD patients are thought to show delayed gastric emptying after ingestion of solid food.[64] However, there are many studies that failed to show a

direct connection between delayed gastric emptying and dyspeptic symptoms,[65-67] suggesting that the relationship may not be entirely clear.

On the other hand, much attention has recently been paid to impaired gastric accommodation, which is also known as adaptive relaxation. The accommodation reflex is a volume response of the upper part of the stomach after a meal. After ingestion of food, the gastric fundus spontaneously dilates and begins to store food. Such impairment of gastric accommodation is known to correlate well with dyspeptic symptoms, especially early satiety.[68,69] However, this relationship has not been confirmed well in studies from some Asian countries.[70,71]

Statement 15. Visceral hypersensitivity is one of the pathophysiologic mechanisms in functional dyspepsia.

Grade of evidence: high.

Level of agreement: a: 100.0%; b: 0%; c: 0%; d: 0%; e: 0%; f: 0%.

Visceral hypersensitivity has been reported to play a key role in the pathophysiology of FD. Several studies have clearly demonstrated that, as a group, patients with FD have enhanced sensitivity to distension of the proximal stomach.[71-73] Abnormal central nervous system processing of visceral stimuli can be involved in hypersensitivity to

proximal gastric distention. Patients with FD, who have hypersensitivity to gastric distension, more often report pain due to hyperalgesia.[74] Pain occurs in hypersensitive dyspeptic patients at distending pressures that induce non-painful sensations. In these patients, various luminal stimuli including chemical and mechanical stimuli can be perceived as unpleasant discomfort or pain. A study from the West reveals that hypersensitivity to gastric distention is found in 34% of patients with FD.[73] A study from Korea showed that 37.5% of Korean patients with FD had hypersensitivity to gastric distension.[71] Although there is a report showing the association of this mechanism with symptoms of postprandial epigastric pain, belching and weight loss,[73] this association has not been clearly established yet, particularly in Asia.[71]

Hypersensitivity to endogenous and exogenous chemicals, gastric acid, or nutrients has been suggested to be associated with dyspeptic symptoms.[75-77] Since patients with visceral hypersensitivity are considered to have enhanced sensory nerve activity, stimulation of luminal chemoreceptors in the upper GI mucosa may generate or aggravate dyspeptic symptoms. However, data on the prevalence and pathogenetic role of hypersensitivity to chemicals and nutrients in Asian patients with FD are lacking.

Statement 16. Psychosocial factors may play a role in functional dyspepsia.

Grade of evidence: moderate.

Level of agreement: a: 84.2%; b: 15.8%; c: 0%; d: 0%; e: 0%; f: 0%.

Psychological disturbances have been proposed as one of the possible causes of FD.[48] Several population-based studies demonstrated that patients with FD have higher prevalence of depression and anxiety compared to control population and even patients with organic dyspepsia.[48,78-80] It was shown that there is a gradual transition from mild to severe psychosocial morbidity parallel with dyspepsia symptom severity,[78,81] and Hsu et al.[82] found that patients fulfilling the criteria for either postprandial distress syndrome or epigastric pain syndrome had psychologically more severe symptoms. In clinical practice, antianxiety or antidepressive agents are sometimes prescribed for symptoms of FD. On the basis of a systemic review of the literature, Hojo et al. concluded that antianxiety agents and antidepressive agents may be effective treatments for FD.[83]

Stressful life events in the patient's social environment are also thought to be associated with the onset or exacerbation of dyspeptic symptoms, although the relationship is still not clear. Some studies have shown that the number of stressful life events experienced by FD patients was more than that experienced by healthy controls,[79,84,85] whereas others have found no significant difference in the number of

such events.[84,86] Hui et al.[86] indicated that differences in FD symptoms correlated with psychological factors such as negative perception of major life events rather than with the number of stressful life events experienced. Chen et al.[87] demonstrated that severity of stressful life events was positively correlated with disturbance of gastric myoelectric activity in FD patients. Coping pattern is a psychological factor associated with FD symptoms.[84,86,88] Several psychological studies have found that effective coping strategies play a role in mitigating anxiety, depression, and somatic problems.[88,89] Cheng et al.[89] designed flexible coping psychotherapy for enhancing coping flexibility of FD patients and demonstrated that the psychotherapy significantly changed FD symptom severity. Lastly, familial factors may include psychological, environmental or genetic factors, which may contribute to abdominal symptoms of FD patients. Ahn et al.[90] found that family function score was lower in an FD group than in a normal control group, and Ochi et al.[91] suggested that parental criticism experienced in early life may underlie the psychological background of FD patients and correlated with their abdominal symptoms. All these results add support to the theory of psychosocial disturbances in the pathogenesis of FD.

Statement 17. Gastric acid may be responsible for the symptoms in a subset of

patients with functional dyspepsia.

Grade of evidence: moderate.

Level of agreement: a: 89.5%, b: 10.5%; c: 0%; d: 0%; e: 0%; f: 0%.

Because anti-secretory therapy is effective in some patients with FD,[92,93] it is thought that gastric acid may play a role in the pathogenesis of FD. However, it has not been clearly demonstrated that excessive gastric acid is a pathogenetic factor in FD, and data on the amount of gastric acid secretion in patients with FD are lacking. Results of studies from Asian countries are controversial.[94-96]

Proton pump inhibitors (PPIs) are believed to be beneficial in a subset of patients with FD. This positive response is mainly confined to patients with ulcer-like and reflux-like dyspepsia.[92] Patients with postprandial pain are reported to have a high prevalence of pathological acid exposure, which suggests that patients who respond to acid-suppressive therapy might have non-erosive reflux disease.[97] Several studies have suggested a role for increased duodenal acid exposure or duodenal or gastric hypersensitivity to acid in the pathogenesis of symptoms in some patients with FD.[76,98-100] These factors might explain the beneficial effects of acid-suppressive treatment for FD. However, the prevalence and pathogenetic role of these abnormalities

in Asian patients with FD remains to be further explored.

Statement 18. *Helicobacter pylori* **may play a role in pathogenesis of functional dyspepsia.**

Grade of evidence: moderate.

Level of agreement: a: 52.6%; b: 31.6%; c: 5.3%; d: 10.5%; e: 0%; f: 0%.

The reported prevalence of *H. pylori* infection in patients with FD varies from 39% to 87%.[101] Several epidemiological studies have shown that *H. pylori* infection occurs more frequently in FD than in matched control populations. A meta-analysis published in 1999 reported a summary odds ratio for *H. pylori* infection in FD of 1.6 (95% CI, 1.4 to 1.8).[102] Mechanistic studies found that *H. pylori*-infected FD patients had higher stimulated gastric acid output than *H. pylori*-negative healthy volunteers.[103] However, no associations between *H. pylori* positivity and symptom pattern, gastric emptying rate, gastric accommodation, or sensitivity to distension in FD patients have been found.[104]

The effect of *H. pylori* eradication on dyspeptic symptoms in FD patients has been evaluated in several large, well-designed, randomized controlled trials, but the results were conflicting.[105,106] Conflicting data have also been reported from Asia.[29,107] Wong et al.[108] found that the standard treatment for *H. pylori* infection is suboptimal in FD

compared with duodenal ulcer. A Cochrane systemic review showed that there was a

10% relative risk reduction in the *H. pylori* eradication group compared to placebo, and

that the number needed to treat to cure one case of dyspepsia was 14.[109] However, a

recently published systemic review and meta-analysis from the Chinese literature found

that the summary odds ratio for improvement in dyspeptic symptoms in patients with

FD after *H. pylori* eradication was 3.61, suggesting that the role of this infection is

much larger in the Chinese population than in Western populations.[110]

Some of the consensus members proposed that dyspepsia accompanied by *H. pylori*

infection should be regarded as a different disease entity from FD. In other words, FD

patients should be *H. pylori*-negative and *H. pylori* infection should be eradicated

before making a diagnosis of FD. The logic behind this opinion was (1) histological

gastritis is no longer a non-organic disease as it can be visually recognized by advanced

endoscopic technologies, such as magnifying or narrow band imaging endoscopy, (2) *H.*

pylori eradication is strongly recommended regardless of the presence of dyspeptic

symptoms, especially in some Asian countries where gastric cancer is highly prevalent,

and (3) the concept of post-infectious FD has already been recognized and *H. pylori*

infection is apparently an infection that causes mucosal inflammation.

Statement 19. Post-infectious functional dyspepsia occurs in a subset of patients.

Grade of evidence: moderate.

Level of agreement: a: 73.7%, b: 26.3%; c: 0%; d: 0%; e: 0%; f: 0%.

FD has been reported to occur in patients following GI infection. In a prospective study from Spain, 14% of persons who were infected by shigella developed post-infectious dyspepsia, resulting in a relative risk of 5.2 compared to controls.[111] Furthermore, a number of reports from Europe and Asia have shown that low-grade inflammation is found in the duodenum of patients with post-infectious FD.[112,113] In a large retrospective tertiary center study, Tack et al.[114] showed that a subset of presumed post-infectious dyspepsia patients had higher prevalence of impaired accommodation of the proximal stomach. There is evidence that post-infectious FD can occur in a subset of patients, and functional abnormalities and persistent inflammation of the gut are found.

Statement 20. Genetic factors may be involved in pathogenesis in a subset of patients with functional dyspepsia.

Grade of evidence: low.

Level of agreement: a: 78.9%, b: 15.8%; c: 5.3%; d: 0%; e: 0%; f: 0%.

The G-protein β3 subunit C825T polymorphism was reported to be associated with dyspepsia in studies from the United States (both CC and TT genotypes with meal-unrelated dyspepsia)[115] and Germany (CC genotype).[116] In contrast, the 825 T allele was suggested to be related to dyspepsia in reports from Japan and the Netherlands.[117-119] In Japanese groups, the following polymorphisms have been reported to be associated with the development of FD or dyspeptic symptoms: IL-17F 7488T, macrophage migration inhibitory factor G-173C,[120] catechol-o-methyltransferase gene val158met,[121] T779C of CCK-1 intron 1,[122] cyclooxygenase-1 T-1676C,[123] p22 phagocyte oxidase component of nicotinamide adenine dinucleotide phosphate oxidase C242T,[124] and transient receptor potential vanilloid 1 G315C.[125] These data indicate that genetic factors are associated with the development of FD. However, the studies from Asia are limited and are only from Japan. Validation in other countries and in a large-scale study is warranted.

Statement 21. Dietary factors and lifestyle may be involved in the pathogenesis of functional dyspepsia.

Grade of evidence: low.

Level of agreement: a: 94.7%, b: 5.3%; c: 0%; d: 0%; e: 0%; f: 0%.

The investigation of lifestyle factors in FD has been limited to a few studies. From Asia, Chen et al.[79] and Mahadeva et al.[44] reported that tea drinking was negatively associated with FD. Theophylline in tea acts as a competitive antagonist to adenosine receptors, which induce epigastric pain and chest pain.[126,127] However, there is little Asian literature on the types and amounts of tea drunk by dyspeptic patients.

More recently, the concept of visceral hypersensitivity to nutrient stimuli, especially hypersensitivity to fat,[128,129] has been highlighted as an etiology of FD.[130,131] Food ingestion is associated with stimulation of secretion of a range of GI hormones, including cholecystokinin and peptide YY, and suppression of ghrelin.[132] It is conceivable that gut peptides play a role in the induction of dyspeptic symptoms in FD patients with nutrient hypersensitivity. In patients with FD, intolerance to specific foods is common and many foods are reported to induce symptoms.[133] On the contrary, chili and rice[134] and ginger[135] are reported to be good for dyspepsia. Feinle-Bisset et al.[136] reported that postprandial fullness is the most severe symptom in patients reporting

aggravation by meal.

Most studies concerning the relationships between lifestyle or dietary factors and FD are based on symptom intensities evaluated by questionnaire or on physiological studies involving particular foods or components. Further prospective studies are necessary to clarify the details of these pathogenetic factors and the role of dietary therapy in the management of FD.

Management

Statement 22. An integrated approach addressing physiological, biological, psychological and social factors is recommended for all patients with functional dyspepsia. (See Fig. 2)

Grade of evidence: low.

Strength of recommendation: probably do it.

Level of agreement: a: 84.2%, b: 10.5%; c: 5.3%; d: 0%; e: 0%; f: 0%.

As the pathogenesis of FD is multi-factorial, treatment should be individualized, with an effort to identify as many possible putative factors as possible. There have been no direct data to support this approach to managing FD in general. On the other hand, there have been studies on IBS that demonstrate a favorable response to treatment when physicians make an effort to address possible contributing factors such as past GI infection (biological), psychosocial stressors (psychological) and dietary changes (social), to reassure the patient by providing reasonable evidence that he or she does not have a life-threatening condition, and to explain the diagnosis with appropriate pathophysiological (physiological) models. In view of the overlap in symptoms, patient

demographics and putative pathophysiology, it is reasonable to recommend a similar approach to FD, as was recommended in the recent Asian IBS Consensus.[137-139]

There is a study to support adopting a combination of intensive medical therapy with psychological intervention in patients with refractory FD. Haag et al.,[140]http://wizfolio.com/?citation=1&ver=3&ItemID=461&UserID=16860&AccessCode =5DDA84B86AD649098C11369F4FF13DCC&CitationSuffix= in a prospective randomized, controlled trial, compared the long-term outcome of intensive medical therapy (with or without cognitive-behavioral or muscle relaxation therapy) versus standard medical therapy in patients with refractory FD and found that in FD patients with refractory symptoms, intensified medical management involving function testing and psychological intervention yielded superior long-term outcomes. There is also a study from China that showed psychological intervention to be superior to prokinetic therapy.[141]

Statement 23. Where socio-economic conditions allow, *Helicobacter pylori* testing and eradication should be part of the management strategy for all patients in Asia who present with dyspepsia. (See Fig. 2)

Grade of evidence: high.

Strength of recommendation: do it.

Level of agreement: a: 58.0%, b: 42.0%; c: 0%; d: 0%; e: 0%; f: 0%.

H. pylori eradication has a statistically significant effect on symptom relief in patients with FD. Cochrane meta-analysis on 17 randomized controlled trials (n=3566) found a small but statistically significant benefit of *H. pylori* eradication therapy at 12 months, with relative risk reduction of 10% (95% CI, 6% to 14%) and number needed to treat of 14 (95% CI, 10 to 25).[109] Studies from Asia included in this meta-analysis showed both positive[142,143]_ENREF_143 _ENREF_143and negative[107,144] results. However, in a recent meta-analysis of 7 Chinese studies,[110] the summary odds ratio for symptom improvement by *H. pylori* eradication was 3.61 (95% CI, 2.62 to 4.98; *P* < 0.0001), which was far higher than those of previously published meta-analyses. Recent studies from Singapore also support the role of *H. pylori* eradication in FD,[145,146] suggesting that the benefit of *H. pylori* eradication therapy is possibly more significant in the Asian region. However, benefits of this strategy should be weighed against its costs including possible induction of high rate of antibiotic resistance in addition to the high financial burden in areas with high prevalence of *H. pylori* infection.

The recently published Asia Pacific consensus guidelines on *H. pylori* infection stated, "*H. pylori* eradication is indicated for *H. pylori*-positive patients with investigated dyspepsia (non-ulcer dyspepsia)."[147] The basis for the recommendation, which was itemized by the guidelines, included the benefit of *H. pylori* eradication from the social aspect. In other words, eradication of *H. pylori* in patients with FD has the additional benefit of reducing the risks for peptic ulcer disease and gastric cancer.

In studies from South America and China, regions with high prevalence rates of *H. pylori* infection and high incidence rates of gastric cancer, *H. pylori* eradication produced significant increases in the rates of regression of intestinal metaplasia and gastric atrophy and lowered the risk of progression to intestinal metaplasia,[148-153] providing evidence that *H. pylori* eradication has a direct impact on gastric cancer occurrence and reduces the risk of metachronous gastric cancer after endoscopic resection. A meta-analysis[154]_ENREF_148 of 6 randomized placebo-controlled *H. pylori* eradication trials[148,151,152,155-157]_ENREF_155 showed that with *H. pylori* eradication, the pooled relative risk of developing gastric cancer was 0.65 (95% CI, 0.43 to 0.98).

Considering all these data, the management algorithm recommended to eradicate *H. pylori* if socioeconomic conditions allow (Fig. 2).

Statement 24. Proton pump inhibitors are effective for controlling symptoms in patients with functional dyspepsia, although supportive data from Asia are lacking. (See Fig. 2)

Grade of evidence: moderate.

Strength of recommendation: do it.

Level of agreement: a: 75.0%, b: 25.0%; c: 0%; d: 0%; e: 0%; f: 0%.

The rationale for using PPIs in FD stems from both clinical as well as physiological perspectives. Studies showing overlap between non-erosive reflux disease (NERD) and FD also support use of PPI in patients with FD.[158-161] Besides this, pathological esophageal acid exposure has been reported in Western FD patients without symptoms of heartburn.[97,162]

To date, 7 randomized controlled trials of PPI versus placebo have been reported.[92,95,163-167] Six of the 7 studies were conducted in Western population and they demonstrated a benefit over placebo for symptom improvement in FD patients,[92,163-167] though PPIs may not be effective in dysmotility-like dyspepsia.[168] In fact, the combined effect of all 7 trials (2387 PPI patients, 1338 placebo patients) was expressed in a recent meta-analysis,[169] which reported that there was a modest but statistically significant

difference in symptom relief in patients receiving PPIs (40.3%) compared with those given placebo (32.7%), and the estimated number needed to treat was 14.6 patients (95% CI, 8.7 to 57.1).

It must be noted that the only trial that showed negative results among the 7 trials in the above-mentioned meta-analysis was from Hong Kong. In addition, a recent randomized trial from Hong Kong that investigated the efficacy of a PPI on *H. pylori*-negative uninvestigated dyspeptic patients (epigastric pain and discomfort) also failed to show an efficacy of PPI over placebo.[96] An open-labelled study from Singapore, also reported only a modest response to PPI.[170] Characteristic differences between Asian and Western patients with FD may explain the lower benefit of PPIs in Asian patients. These data suggest that the efficacy of PPIs in patients with FD needs to be reevaluated in the Asian population.

Statement 25. High-dose proton pump inhibitor therapy is not superior to standard doses for symptom control in functional dyspepsia.

Grade of evidence: moderate.

Strength of recommendation: probably don't do it.

Level of agreement: a: 65.0%, b: 25.0%; c: 10.0%; d: 0%; e: 0%; f: 0%.

Several studies have examined the role of standard and higher doses of PPI in the treatment of FD.[95,164-166,168] Whether the patients responded to PPIs or not, these studies, which involved a large number of patients, consistently found no difference in symptom response between standard and higher PPI doses. A recent meta-analysis also concluded that the dose of PPI did not influence the response of FD symptoms to treatment.[169] It is therefore proposed that a standard dose of PPI is sufficient in the management of FD, and that dose escalation is unlikely to further reduce symptoms.

Another concern regarding the use of higher doses of PPI in patients with FD relates to incurring unwanted problems caused by acid inhibition. Recent studies of healthy, asymptomatic volunteers who received PPI treatment for either 4 or 8 weeks demonstrated rebound acid hypersecretion following withdrawal of the PPI, resulting in the development of dyspeptic symptoms after PPI treatment.[171,172] Yet another concern regarding PPI administration relates to the development of small intestinal bacterial overgrowth (SIBO) in patients receiving long-term therapy.[173] Although long-term PPI therapy has not been advocated in FD, the risk of SIBO may be greater in patients on higher PPI doses than in patients on standard PPI doses.[173]

Statement 26. Prokinetics may provide symptom relief in some functional dyspepsia patients. (See Fig. 2)

Grade of evidence: moderate.

Strength of recommendation: do it.

Level of agreement: a: 90.0%, b: 10.0%; c: 0%; d: 0%; e: 0%; f: 0%.

Prokinetic agents, such as metoclopramide, domperidone, trimebutine, cisapride, itopride, mosapride, levosulpiride and cinitapride, can stimulate digestive tract motility via different mechanisms of action. Use of cisapride is currently restricted in most Asian countries because of its cardiovascular complications. Because delayed gastric emptying is considered a potential contributing factor to FD symptoms, prokinetic agents are often used in FD. In a meta-analysis from the Cochrane library that included 24 randomized controlled trials with 3178 patients, the efficacy of prokinetics was superior to placebo (57% vs. 47%).[93] However, studies on prokinetics in FD had limitations due to the high degree of heterogenicity and small sample size.[93,174]

The clinical trial data for the new drug acotiamide showed a clear margin of symptom improvement compared with placebo, and may be approved for FD of the postprandial distress syndrome subtype.[175,176]

Statement 27. Some studies from Asia reported that herbal medications provide symptom relief in functional dyspepsia. (See Fig. 2)

Grade of evidence: moderate.

Strength of recommendation: probably do it.

Level of agreement: a: 60.0%, b: 40.0%; c: 0%; d: 0%; e: 0%; f: 0%.

Limited studies have shown potential benefit of herbal medicines for symptom relief in FD patients. In a meta-analysis that included 33 studies of the efficacy of xiaoyao san (XS),[177] a well-known traditional Chinese herbal formula for FD treatment, modified XS without (OR 3.26; 95% CI, 2.24 to 4.47) or with (OR 4.32; 95% CI, 2.64 to 7.08) prokinetics significantly reduced symptoms compared with prokinetics alone. However, the reporting of quality issues in these studies was generally poor. These studies are usually non-randomized, non-blinded and without placebo control. Therefore, high-quality controlled trials are required to assess the effects of XS in comparison to placebo. Another relatively small-scaled but placebo-controlled study from Japan demonstrated the efficacy of the Japanese herbal medicine rikkunshito (TJ-43) in reducing GI symptoms in FD patients and accelerating gastric emptying.[178] This

medicine was found to improve gastric accommodation in a study using extracorporeal ultrasonography.[179]

Statement 28. Anti-depressant and anxiolytic agents have a role in the management of functional dyspepsia, despite the limited evidence. (See Fig. 2)

Grade of evidence: low.

Strength of recommendation: probably do it.

Level of agreement: a: 80.0%, b: 20.0%; c: 0%; d: 0%; e: 0%; f: 0%.

Evidence supporting the use of psychotherapy in treatment of FD is inconsistent and weak.[180] As for pharmacological therapies, only limited studies of antidepressants or anxiolytic drugs are available. In a small study involving only 7 FD patients with sleep disturbance, low-dose amitriptyline improved dyspeptic symptoms more than placebo did.[181]_ENREF_179 In a series of studies from Dublin, buspirone, a partial $5HT_{1A}$ agonist with antidepressant and anxiolytic effects, was shown to improve dyspeptic symptoms in FD, with associated enhanced prolactin release in FD patients compared with controls, suggesting that central HT_{1A} receptors may be supersensitive in FD patients.[182-184] A recent study from Japan showed that symptom resolution was

significantly greater in FD patients treated with tandospirone, a $5TH_{1A}$ agonist with anxiolytic activity, than in patients given a placebo.[185] On the contrary, venlafaxine, a serotonin and norepinephrine reuptake inhibitor, failed to show positive results and a greater number of patients on venlafaxine than on placebo dropped out of the study because of side effects.[186]

Central factors, such as psychological disturbance, sleep disturbance and central serotonin receptor sensitivity, may be important determinants of response to anti-depressant treatment in FD patients. In an open-label study from Taiwan, fluoxetine improved GI symptoms in depressed but not in non-depressed FD patients,[187] and in a study from Norway, high levels of neuroticism and concealed aggressiveness predicted poor response to mianserin, a tetracyclic antidepressant.[188]

Statement 29. Specific food ingredients such as chili, spice and fats may provoke dyspeptic symptoms. Dietary modification can be considered in functional dyspepsia but data are lacking. (See Fig. 2)

Grade of evidence: low.

Strength of recommendation: probably do it.

Level of agreement: a: 80.0%, b: 20.0%; c: 0%; d: 0%; e: 0%; f: 0%.

Although patients frequently believe that certain foods are the cause of their symptoms, there are few good studies to exclude the effect of psychological bias in the patient's perception. However, experimental studies suggest that certain food ingredients such as chili, spice and fats may provoke dyspeptic symptoms. Most importantly, there is no well-controlled study to demonstrate that dietary exclusion of specific food ingredients is effective for symptom control in FD. [45,128,129,133,134,136,189-196] _ENREF_178

Conclusion

This consensus was developed to attract attention to such data from Asian countries, to articulate the experience and views of Asian experts, and to provide a relevant guide on management of FD for primary care physicians working in Asia. This consensus shows distinctive features of FD in Asia and will provide a guide to the diagnosis and management of FD for Asian primary care physicians. The understanding of FD is still incomplete and is evolving over time and this consensus report will be revised as our understanding of FD grows.

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Figure Legends

Figure 1. Diagnostic algorithm for functional dyspepsia in Asian primary care settings.

a: Dyspepsia refers to a symptom or set of symptoms that are considered to originate from the gastroduodenal region. The dyspeptic symptoms are epigastric pain, epigastric burning, postprandial fullness, early satiation and other symptoms including bloating in the upper abdomen, nausea, vomiting and belching. Chronic dyspeptic symptoms can be continuous, intermittent or recurrent. More than two thirds of the consensus members agreed that symptom duration of 3 months or longer might be enough.

b: The alarm features are unintended weight loss, progressive dysphagia, recurrent or persistent vomiting, evidence of gastrointestinal bleeding, anemia, fever, family history of gastric cancer, new onset dyspepsia in the subjects over 40 years of age in population with high prevalence of upper gastrointestinal malignancy and over 45 and 50 years in populations with intermediate and low prevalence, respectively.

c: The appropriate choice from the three options depends on patient's symptom profiles, patient's wish, local risk of *Helicobacter pylori* (*H. pylori*) infection and gastric cancer as well as local health care or re-imbursement system.

Figure 2. Management algorithm for functional dyspepsia in Asian primary care settings.

a: Where socio-economic conditions allow, *Helicobacter pylori* (*H. pylori*) test and eradication should be part of the management strategy for all patients presenting with dyspepsia in Asia.
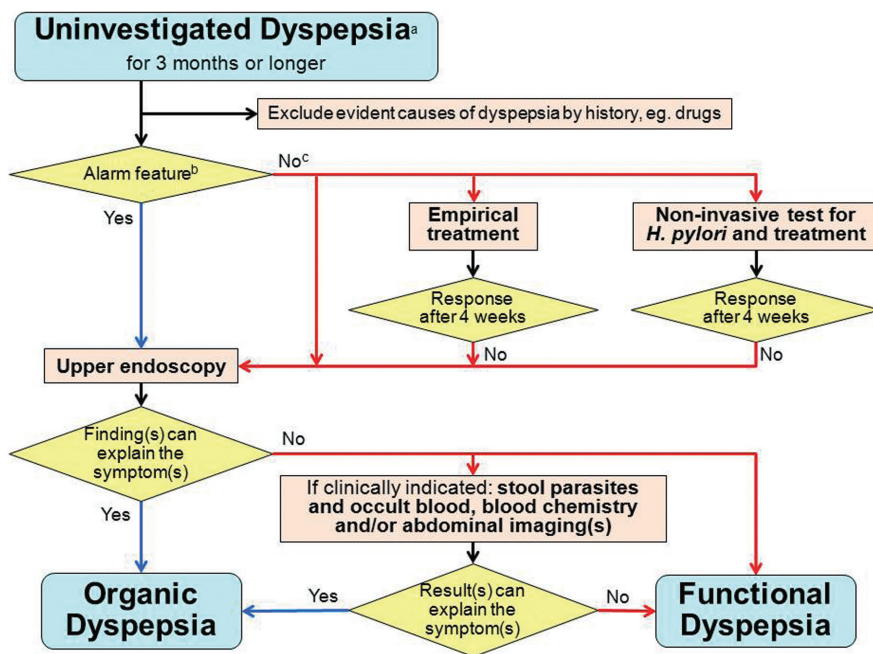
b: Specific food ingredients may provoke dyspeptic symptoms. Dietary modification can be considered in functional dyspepsia but data are lacking.

c: Where there is any available herbal medication previously validated, it may be tried.
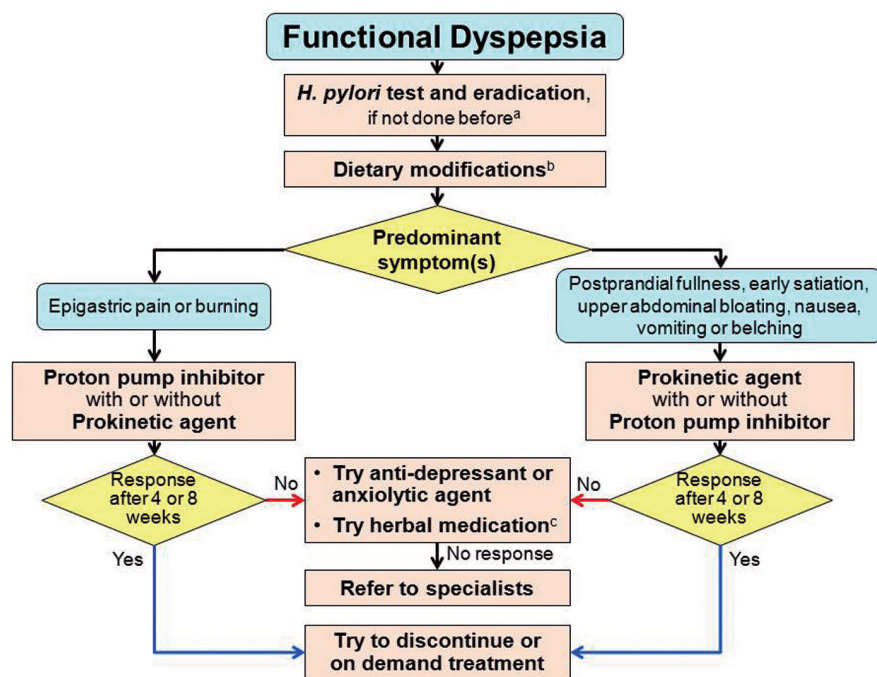
Table 1. Grade of Evidence, Level of Agreement and Strength of Recommendation

Category	Description
Grade of evidence	
High	Further research is unlikely to change our confidence in the estimate of effect
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and might change the estimate
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
Very low	Any estimate of effect is very uncertain
Level of agreement†	
a	Accept completely
b	Accept with minor reservation
c	Accept with major reservation
d	Reject with major reservation
e	Reject with minor reservation
f	Reject completely
Strength of recommendation	
Do it	A judgment that most well-informed people would make
Probably do it	A judgment that a majority of well-informed people would make but a substantial minority would not
Probably not do it	A judgment that a majority of well-informed people would make but a substantial minority would not
Not do it	A judgment that most well-informed people would make

†Each statement was accepted when 80% or more of participants voted a or b.

Uninvestigated Dyspepsia[a]
for 3 months or longer

Exclude evident causes of dyspepsia by history, eg. drugs

Alarm feature[b]

No[c]

Yes

Empirical treatment

Non-invasive test for *H. pylori* and treatment

Response after 4 weeks

Response after 4 weeks

No

No

Upper endoscopy

Finding(s) can explain the symptom(s)

No

Yes

If clinically indicated: **stool parasites and occult blood, blood chemistry and/or abdominal imaging(s)**

Organic Dyspepsia

Yes

Result(s) can explain the symptom(s)

No

Functional Dyspepsia

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Functional Dyspepsia

H. pylori test and eradication, if not done before[a]

Dietary modifications[b]

Predominant symptom(s)

Epigastric pain or burning

Postprandial fullness, early satiation, upper abdominal bloating, nausea, vomiting or belching

Proton pump inhibitor with or without **Prokinetic agent**

Prokinetic agent with or without **Proton pump inhibitor**

Response after 4 or 8 weeks

Response after 4 or 8 weeks

No → No

- **Try anti-depressant or anxiolytic agent**
- **Try herbal medication**[c]

No response

Refer to specialists

Yes — Yes

Try to discontinue or on demand treatment

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