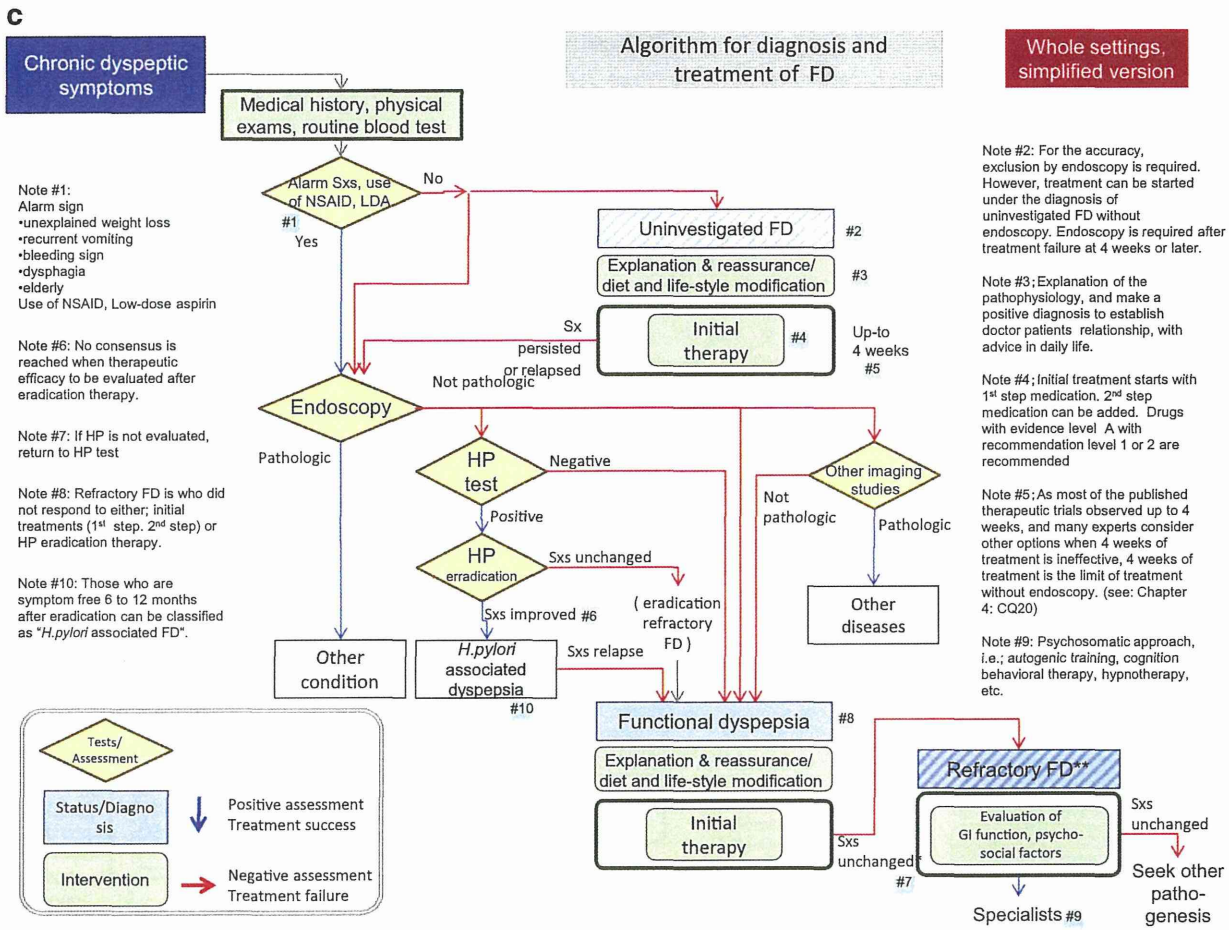

Fig. 1 continued

have persisted for at least 3 months, and the initial symptoms must have appeared at least 6 months previously [1]. However, perhaps because almost all Japanese people have health insurance coverage, patients generally visit a medical facility within a month of symptom onset. As a result, most Japanese patients do not meet the Rome III criteria for duration of symptoms (onset at least 6 months previously and symptoms persisting for at least 3 months) and therefore cannot be diagnosed with functional dyspepsia under those criteria [2, 3].

The new Japanese guidelines contain a general definition, and rely on the clinical physician to decide whether the patient's symptoms qualify as dyspepsia and whether those symptoms are chronic. Until recently, most functional dyspepsia patients in Japan have been diagnosed with and treated for chronic gastritis. However, chronic gastritis intrinsically involves histological inflammation of the gastric mucosa, and the diagnosis is unaffected by the presence or absence of symptoms. Gastritis is thus in a completely different diagnostic class from functional dyspepsia, which is diagnosed from symptoms. The use of these two very different names for the diagnosis of the two conditions should help to reduce confusion.

Prevalence of FD

- The prevalence of functional dyspepsia in Japanese patients ranges from 11 to 17 % in subjects who have medical checkups and from 45 to 53 % in patients who seek medical care because of upper gastrointestinal symptoms.
- Because of the absence of reliable data, it is difficult to determine whether the prevalence of Japanese patients with functional dyspepsia is increasing.

Comment: Although results for the prevalence of FD in Japanese patients varied according to the definition used in each research project, differences were not significant (Table 2) [4–10]. An epidemiological study on the prevalence of FD in Western countries showed findings of 14.7 % in North Europe, 15 % in the USA, and 23.8 % in the UK [11]. These results suggest that the prevalence of

Table 1 Diagnostic tests used to diagnose FD depending on the level of clinical practice

	CQ	Grade	EvL	PCP	GI specialists	Research institute
History taking (Medical interview)				●	●	●
Self-administered questionnaire	2-2	na		△	△	△
Physical examination	2-7	na		●	●	●
Inquire use of NSAID, LDA	2-9	na		●	●	●
CBC & blood biochemistry	2-7	na		●	●	●
Serology for Inflammation	2-7	na		●	●	●
Fecal occult blood	2-7	na		●	●	●
Abdominal XP	2-2	na		●	●	●
EGD	2-1	2	B	△	●	●
H.pylori test	2-6	1	A	△	●	●
Ba swallows 推	2-2	na		△	△	●
Abdonimal US study	2-2	na		△	△	●
Abdominal CT scans	2-2	na			△	●
GI function tests**	2-2	na				●
Evaluation of psycho-social factors	2-5	1	C	△	△	●

EvL: evidence level
na: not available
LDA: low dose aspirin

PCP: Primary Care Physician
△: Perform if possible
●: Recommend to perform
*: Modalities may vary depend on institutions

Table 2 The reported prevalence of FD in Japanese patients

References	Years	Study design	Definition of FD	Subjects	Number	Prevalence (%)
Kinoshita [4]	1992	Cross-sectional study	NUD (AGA working group)	Outpatients	106	53
Schlemper et al. [5]	1993	Cross-sectional study	NUD (AGA working group)	Medical checkup	731	13
Hirakawa et al. [6]	1999	Cross-sectional study	NUD (AGA working group)	Medical checkup	1,139	17
Kawamura et al. [7]	2000	Cross-sectional study	Rome criteria (1991)	Medical checkup	907	11
Kawamura et al. [8]	2001	Cross-sectional study	Rome II	Medical checkup	2,263	
				Dysmotility		8.9
				Ulcer-like		5.2
Kaji et al. [9]	2010	Cross-sectional study	Rome III	Medical checkup	2,680	10
Okumura et al. [10]	2010	Cross-sectional study	Rome III (partially modified)	Outpatients	381	44.6

NUD non-ulcer dyspepsia, *AGA* American Gastroenterological Association

FD in Japan is lower than in the West. Only limited data are available on changes in HD prevalence, although risk factors for FD seem to be increasing.

Gender, BMI, age, and FD

- Women are reported to be more prone to FD than men, although only limited data are available in Japan.
- The relationship between FD prevalence and body mass index remains highly controversial.
- Many data suggest that FD is more prevalent in younger persons than in the elderly, although these findings remain controversial in Japan.

Comment: Considerable epidemiological data are available about gender, obesity, age, and FD [12, 13], although those data have been reported primarily from Western countries. In addition, unfortunately, inconsistent results have been obtained on the relationship between the prevalence of FD and body mass index (BMI) because different criteria were used for FD. Furthermore, FD is a multifactorial disease, so results could also be influenced by factors other than BMI, including sociopsychological stress. In addition, differences still remain between Japan and Western countries with regard to several environmental factors, including lifestyle and diet, so data from Western countries are not always applicable to Japanese FD patients.

Consultation behavior

- Patient behavior with regard to first clinic visit is not influenced by the duration of FD, but resistance to return visits is related to the duration of symptoms.

Comment: Patient consultation behavior with regard to the first clinic visit is determined not only by the patient's quality of life but also by personality, mental state, and health insurance status. Two studies from Japan suggested that patient behavior with regard to the first clinic visit was not influenced by the duration of FD [2, 3]. In an earlier European study, FD patients from Denmark, France, Germany, Netherlands, Hungary, and Poland were followed up for 3 months after a 4-week treatment trial with proton pump inhibitors or placebo. Results from that study revealed that symptom resolution in FD patients had a positive impact on quality of life and reduced subsequent costs for a 3-month period after cessation of initial treatment because the patient resisted returning to the clinic [14]. Those findings suggest that FD patients are more likely to return to the clinic if their FD symptoms continue despite treatment.

Quality of life in FD

- FD patients have impaired quality of life.
- The intensity of FD symptoms is related to the extent of impairment of quality of life.
- The duration of FD is not always related to the extent of impairment of quality of life.

Comment: There have been many studies to evaluate the quality of life (QOL) in FD patients by using several kinds of QOL assessment tools, with consistent results [9, 15, 16]. Several studies have also shown a clear correlation between severity of symptoms and negative impact on QOL. The clinical course of FD is not well known, but interestingly, there have been reports of some FD patients whose symptoms resolved naturally in a clinical situation. Although the available data remain insufficient, two recent studies have indicated that the duration of FD is not related to the extent of impairment of QOL [2, 17]. Accordingly, since the current data are inconclusive, this statement notes that QOL is not always related to the duration of FD.

Pathophysiology

Gastric motility abnormality and visceral hypersensitivity

- Multiple factors seem to be involved in the pathogenesis of FD.
- Disturbance of gastric accommodation is involved in the pathogenesis of FD.
- Disturbance of gastric emptying is involved in the pathogenesis of FD.
- Since hypersensitivity has been demonstrated by stimulation through gastric distention and infusions of acid and lipid into the duodenum, visceral hypersensitivity is involved in the pathogenesis of FD.

Comment: Multiple factors may be associated with the pathophysiology of functional dyspepsia. These factors can include impaired gastric accommodation, delayed gastric emptying, hypersensitivity, social factors, *H. pylori* infection, gastric acid secretion, genetic factors, psychological factors (anxiety or history of abuse), history of infectious colitis, lifestyle (including alcohol consumption and smoking), and morphology of the stomach (cascade stomach).

Both impaired gastric accommodation and delayed gastric emptying are classified as gastric motility abnormality. A close relationship has been reported between symptoms and impaired gastric accommodation, although full consensus has not yet been reached. Recently, results from a randomized, double-blind, placebo-controlled study showed a close relationship between restoration of impaired gastric accommodation and symptomatic relief [18]. Several reports suggest that gastric emptying is impaired in some FD patients, and a meta-analysis indicates that gastric emptying is significantly delayed in almost 40 % of patients with FD [19]. Most studies failed to find a convincing relationship between delayed gastric emptying and symptom pattern, and some studies reported rapid gastric emptying after meals [20] in some FD patients. Visceral hypersensitivity is also regarded as a pathophysiologic factor, and hypersensitivity has been reported to gastric distension [21] and to acid and fat infusion to the duodenum [22].

Psychosocial factors and acid

- Psychosocial factors contribute to symptoms in FD.
- The presence of gastric acid is thought to be a cause of FD, because dyspeptic symptoms can be reduced by acid blockers and because acid affects gastrointestinal motility and sensitivity.

Comment: FD patients scored higher than average for psychosocial factors, and major anxiety was significantly associated with FD and postprandial distress syndrome (PDS) in patients. Findings from a meta-analysis showed a moderate correlation between non-ulcer dyspepsia and depression and anxiety, and the non-ulcer dyspepsia group had significantly more frequent episodes of depression and anxiety disorder than the control group [23]. In population-

based studies, anxiety disorder was the condition most strongly associated with gastrointestinal symptoms [24].

The efficacy of acid blockers for dyspeptic symptoms has been demonstrated in a few meta-analyses [25]. Additionally, acid infusion into the stomach has been reported to induce dysmotility-like predominantly dyspeptic symptoms in healthy Japanese control subjects [26]. Duodenal acidification induces proximal gastric relaxation, increases sensitivity to gastric distension, and inhibits gastric accommodation during and immediately after a meal [27]. These findings suggest that acid plays a role in the pathogenesis of functional dyspepsia.

H. pylori infection

- Since eradication treatment for *H. pylori* improves dyspeptic symptoms in a subset of FD patients, there is a relationship between *H. pylori* infection and FD.

Comment: There is room for argument about the relationship between *H. pylori* infection and functional dyspepsia. Although *H. pylori* infection induces chronic inflammation and changes mucosal morphology and the function of acid secretion, the effects of *H. pylori* on gastric motility and sensation remain unclear. However, a systematic review of randomized controlled trials revealed a 10 % relative risk reduction in the *H. pylori* eradication group compared to the placebo group [28]. Therefore, *H. pylori* infection is associated with pathogenesis in a subset of functional dyspepsia. A global consensus on *H. pylori*-associated dyspepsia is under discussion. Patients whose dyspeptic symptoms are improved by *H. pylori* eradication should not be diagnosed with functional dyspepsia [29] and this condition may be labeled as *H. pylori*-associated dyspepsia.

Genetics and early life events

- There is a possibility that family history and genetic polymorphisms are associated with FD.
- In some cases, a history of abuse in childhood and/or adolescence is associated with FD.

Comment: An association has been reported between the development of functional dyspepsia, family history, and genetic polymorphisms such as C825T of G-protein beta3, T1675C of cyclooxygenase-1, and G315C of TRPV1 [30, 31]. A relationship between functional dyspepsia and a history of abuse in childhood and adolescence has also been reported.

Postinfectious FD

- FD following acute gastroenteritis is also observed in Japan.

Comment: In some cases of infectious gastroenteritis accompanied by fever, diarrhea, nausea, vomiting, and positive stool culture, studies have shown that FD symptoms persist long after the elimination of the causative pathogens [32, 33]. Postinfectious FD is associated with early satiety, weight loss, and nausea [34]. Infiltration by duodenal inflammatory cells such as eosinophils, mast cells, and macrophages may play an important role in the pathophysiology of postinfectious FD patients [33].

Other pathophysiological factors of FD

- Smoking, alcohol intake, and sleep disorders are associated with symptoms of FD.
- Intake of a high-fat diet aggravates clinical symptoms of FD.
- Cascade stomach is associated with dyspeptic symptoms.

Comment: Some studies have reported that smoking aggravates FD symptoms and that alcohol intake and sleep disorders are associated with FD symptoms in Japanese populations [35, 36]. A previous study reported that high fat intake induces nausea and abdominal pain in FD patients compared to healthy volunteers [37]. High fat intake was also reported to be associated with abdominal fullness in FD patients. Although FD patients have a tendency to consume less fat during the day, there is a significant increase in their intake of fat at night. The consumption of spicy foods and capsaicin also affects FD symptoms [38]. Poor eating habits, such as skipping breakfast or lunch and snacking while performing other tasks, could be involved in the symptomatology of FD. The shape of the stomach is considered to be a risk factor in the pathophysiology of FD patients, and cascade stomach is reported to be associated with FD symptoms [39].

Diagnosis

Diagnostic modalities for FD

- Since FD is a diagnosis of exclusion, upper endoscopy should be considered for patients during the clinical course. [Recommendation 2 (100 %), evidence level B].
- Imaging modalities other than endoscopy are recommended for diagnosis of FD. [Recommendation 2 (90 %), evidence level C].

Comment: A diagnosis of FD is established by evaluation of symptoms and exclusion of organic disease, including gastric cancer. Endoscopy is recommended for exclusion of organic dyspepsia because symptomatic criteria do not

distinguish between functional and organic dyspepsia [40]. However, endoscopic examination is not available in some primary clinical settings, so we made endoscopy a level 2 recommendation. This allows patients in those settings to be treated initially without endoscopy (see algorithm for primary care setting).

Imaging modalities including ultrasonography and scintigraphy are useful not only for providing an excluded diagnosis of organic dyspepsia, but also for evaluation of gastrointestinal function [41, 42]. However, assessment of gastrointestinal functionality using imaging modalities is not covered by national health insurance, and is not strongly recommended.

Biomarkers

- At present, there are no clinically useful biomarkers for the diagnosis of FD.

Comment: Many biomarkers, including plasma ghrelin and several gene polymorphisms [43], have been reported to play a role in the pathophysiology of FD. However, most of them are not practical for use except in highly specialized centers, or do not constitute a sufficiently accurate predictor of the diagnosis of FD.

A self-reporting questionnaire

- A self-reporting questionnaire is useful for symptom assessment and is necessary for the management of FD patients. [Recommendation 2 (100 %), evidence level B].

Comment: There are many self-reporting questionnaires, including the GSRS [44] and the Izumo scale [45], which are often used in Japan as well as overseas. These questionnaires are very useful not only for the diagnosis of FD but for the evaluation of treatment efficacy in FD.

Evaluation of psychosocial factors and *H. pylori* infection

- The evaluation of psychosocial factors is recommended for the management of FD patients. [Recommendation 1 (100 %), evidence level C].
- Assessment of *H. pylori* infection is recommended for the diagnosis of FD. [Recommendation 1 (100 %), evidence level A].

Comment: Psychosocial factors have been proposed as an element in the pathophysiology of FD; there seems to be a relationship between anxiety, depression, and FD. It is important to evaluate these factors in clinical practice, and psychosomatic intervention including stress management may be necessary in both the diagnosis and the treatment of FD patients.

Many studies have investigated the association between *H. pylori* infection and dyspeptic symptoms or pathophysiologic mechanisms in FD. However, the effect of *H. pylori* infection on FD remains controversial, and the role of *H. pylori* eradication in FD patients is still uncertain. The US guidelines for the management of dyspepsia recommend *H. pylori* eradication for *H. pylori*-positive FD patients. It is at least necessary to assess *H. pylori* infection in the management of FD patients.

Alarm signs

- An alarm sign is considered to be any sign that raises suspicion of an organic disease. [Recommendation 2 (100 %), evidence level B].

Comment: No difference in the incidence of alarm signs has been reported between organic diseases and FD [46]. If an alarm sign is noted, organic disease should be suspected. However, the absence of alarm signs does not exclude the possibility of organic disease.

Gastrointestinal function testing

- Gastrointestinal function testing is not widely available, and the test results do not necessarily agree with pathogenesis or improve the therapeutic predictability of functional gastrointestinal disorders. The usefulness of such testing in clinical practice thus remains unclear at present.

Comment: In a subset of patients, gastrointestinal function testing could identify symptom-generating pathogenesis such as disorders of gastric emptying or gastric accommodation, and could provide useful information for selection of the best therapeutic option. However, such testing is only performed at specialized medical centers.

NSAIDs, LDA, and FD

- A diagnosis of FD is excluded if the patient is using NSAIDs or low-dose aspirin (LDA) and the symptoms are reduced or eliminated when that use is discontinued.

Comment: Findings from a meta-analysis showed significantly increased prevalence of dyspeptic symptoms after NSAID administration [47]. Patients who are taking NSAIDs or LDA should not be diagnosed with FD.

Evaluation of the severity of FD

- Findings from a questionnaire to evaluate disease severity may predict therapeutic response and potential improvement in QOL.

Comment: The evaluation of symptom severity, based on findings from a patient questionnaire, could predict therapeutic resistance [48] and QOL [49].

Treatment

General concept of the treatment of FD

- To obtain the satisfactory relief of symptoms is an important objective in the treatment of FD. [Recommendation NA, evidence level B].
- Placebo may have a profound effect on the treatment of FD. [Recommendation NA, evidence level A].
- The efficacy of placebo does not differ between men and women. [Recommendation NA, evidence level C].
- Building a favorable patient–doctor relationship is effective for controlling symptoms in patients with FD. [Recommendation 1 (100 %), evidence level B].
- Lifestyle guidance and dietary treatment are effective for FD. [Recommendation 1 (100 %), evidence level B].

Comment: "Satisfactory or adequate relief of symptoms" has been used as an acceptable primary endpoint in several clinical trials to treat patients with functional gastrointestinal disorders [50], and has also served as a useful endpoint in a clinical trial to treat patients with FD [51].

The placebo effect is known to be larger for FD than for other organic diseases of the gastrointestinal tract. One report showed that the mean placebo effect in the treatment of FD was approximately 56 %, but other reports cited a wide range (5–90 %) [25]. Research also suggests that the effect of a placebo appears to be greater for FD than for Crohn's disease (18 %) and ulcerative colitis (9.1 %) [52, 53]. In particular, a full explanation of FD, including the unlikelihood of cancer, may relieve FD patients and result in symptomatic improvement, which in turn may contribute to and increase the placebo effect.

Two cohort studies using the data from placebo arms in double-blinded, placebo-controlled studies showed no gender-based differences in placebo response. Reported factors of lower placebo response rate include a consistent predominant symptom pattern, lower body mass index, and smoking [54, 55]. The importance of building a favorable patient–doctor relationship for treating patients with functional gastrointestinal disorder has been described in Rome III [56] and has been acknowledged by several experts [57]. This relationship is an undoubted fundamental in medicine. It is also likely that changes in lifestyle and dietary habits can be useful in the management of FD. Pilichiewicz et al. [37] suggested the possibility that the FD symptoms in part might be diminished by avoiding a high fat diet. FD patients may tend to avoid eating properly [36], and may benefit from lifestyle guidance and dietary treatment. The Rome III criteria also describe the usefulness of dietary treatment.

First-line treatment of FD

- Acid suppressants are effective for the treatment of patients with FD. [Recommendation 1 (91 %), evidence level A].
- Proton pump inhibitors (PPIs) and histamine type 2 receptor antagonists (H2RAs) provide the same level of efficacy, and both are effective for the treatment of FD. [Recommendation NA, evidence level A].
- Prokinetics are effective for controlling symptoms in patients with FD. [Recommendation 1 (91 %), evidence level A].
- *H. pylori* eradication therapy is effective for a subgroup of *H. pylori*-positive FD patients. [Recommendation 1 (91 %), evidence level A].

Comment: The Cochrane database systematic review in 2006 showed the response rate for H2RA to be 22 % over placebo and PPIs to be 14 % over placebo in patients with non-ulcer dyspepsia. However, there are few reports of acid suppressants in the treatment of patients with FD as diagnosed by the Rome III criteria. Further studies will be needed using Rome III criteria, though these meta-analyses suggest that acid suppressants are effective for the treatment of patients with FD. The Cochrane review concluded that there were no differences in the effects of PPI and H2RA [25]. However, no clinical trials have assessed that difference using the Rome III criteria.

Some meta-analyses have reported the usefulness of prokinetics, although effectiveness has been somewhat inconsistent. Several prokinetics are available in Japan. Of those, only acotiamide, a kind of anticholinesterase inhibitor, has been approved by Japanese health insurance for the treatment of meal-related symptoms of FD. The effectiveness of acotiamide over placebo has been proven in several randomized controlled trials (RCTs) conducted under good clinical practice (GCP) guidelines [36, 58].

A study of *H. pylori* infection, including patients who met the Rome III criteria, demonstrated that symptoms were improved by eradication therapy [59]. And one single-arm short-term study in patients who met Rome III criteria demonstrated that efficacy of eradication therapy was recognized only for epigastric pain syndrome and not

for postprandial distress syndrome [60]. The recent systematic review showed that eradication therapy provided a small but significant improvement in symptoms; those findings were consistent with previous systematic reviews [61]. Since there is no "heroic drug" for FD as of yet, eradication therapy provides a useful treatment option even though its effect is small.

As noted above, these two drugs (either acid suppressants or prokinetics) are recommended as first-line treatment for FD. Eradication therapy for *H. pylori* infection should also be regarded as first-line treatment. However, because this treatment is recommended for all infected subjects, even if they are asymptomatic, we have positioned it separately in the treatment algorithm.

Second-line treatment of FD

- Some herbal medicines are effective for the treatment of patients with FD. [Recommendation 2 (100 %), evidence level A].
- Some antidepressants and anxiolytics are effective for the treatment of patients with FD. [Recommendation 2 (100 %), evidence level A].

Comment: There is some evidence for the therapeutic efficacy of Rikkunshito, a Japanese herbal medicine, for improving gastrointestinal motility disorders in the treatment of FD. Recently, a review article described the basic science and clinical evidence for such use, and discussed future applications for various kampo medicines in the treatment of gastrointestinal tract disorders [62].

In Japan, an RCT was done on the efficacy of tandospirone citrate (a 5-HT1A agonist) in improving symptoms of patients with FD [63]. In addition, two meta-analyses have shown the efficacy of antidepressants and anxiolytics in the treatment of FD patients [64, 65]. However, as of this writing only a few reports describe large-scale randomized clinical trials using these psychiatric drugs for FD.

As noted above, these drugs (antidepressants, anxiolytics, and some herbal medicines) should be used for the second-line treatment of FD if first-line therapy fails to cure or improve dyspeptic symptoms.

Alternative or complementary therapy for FD

- The efficacy of antacids, prostaglandin analogues (misoprostol), and gastroprotective agents (sucralfate and rebamipide) for the treatment of FD has not been proven. [Recommendation NA, evidence level B].
- Combination drug therapy is sometimes performed to control symptoms in patients with FD, although supportive data are lacking. [Recommendation NA, evidence level NA].
- Cognition behavior therapy is effective for controlling symptoms in patients with FD. [Recommendation 2 (100 %), evidence level B].
- There is no definitive evidence about the efficacy of autogenic training for the autonomic nervous system in the treatment of patients with FD. [Recommendation NA, evidence level NA].
- Hypnotherapy is effective for FD, and is recommended. [Recommendation 2 (100 %), evidence level B].
- The efficacy of transcutaneous electroacupuncture has been reported but not confirmed. There have been no clinical trials on the effect of moxibustion. [Recommendation NA, evidence level D].

Comment: The Cochrane review noted no effect from prostaglandin analogues and gastroprotective agents [25]. After that review, the efficacy of rebamipide was assessed in double-blinded, placebo-controlled studies. However, one study from the USA was terminated before it reached the planned sample size [66], and one study from Japan showed no effect [67], suggesting that the effectiveness of these drugs is not yet clear. Combination drug therapy is sometimes performed to control symptoms in patients with FD in clinical practice, but there is little evidence of usefulness. Since the pathophysiology of FD is multifaceted, combination therapy with drugs that target different causes might be effective. Further study is needed on this issue.

A randomized clinical trial showed that cognition behavior therapy was effective in patients with FD, but the sample size was relatively small [68], and other information on this issue is limited. A few cross-sectional and case–control studies have been conducted on the association between imbalance of the autonomic nervous system and the pathogenesis of FD [69, 70]. However, no efficacy has been proven, either for the drugs described above or for autogenic training for autonomic nervous system intervention. Few studies confirm the effectiveness of hypnotherapy, although their results suggest that hypnotherapy may be more effective than drug therapy for the treatment of FD [71]. One study showed the efficacy of transcutaneous electroacupuncture in the treatment of FD [72], but in another study the results of classical six-point manual acupuncture could not be differentiated from the placebo [73]. Neither transcutaneous electroacupuncture nor manual acupuncture is widely practiced in Japan, and no studies have been reported.

If the above recommended first-line and second-line regimens are unsuccessful, FD patients may undergo alternative or complementary therapies as a further step in the treatment regimen. However, little definitive evidence is available in Japan on such therapies, and their efficacy has not been established thus far.

Other statements

- Treatment of FD based on its subtypes of the Rome III criteria may be appropriate. [Recommendation 2 (90 %), evidence level A].
- Whether or not patients who suffer from dyspeptic symptoms for years are resistant to FD treatment is still unclear. [Recommendation NA, evidence level NA].
- The recommendation period to change the treatment for refractory FD is around 4 weeks. [Recommendation 2 (70 %), evidence level C].
- Drug treatment can be ceased after the disappearance of symptoms. [Recommendation 2 (80 %), evidence level C].

Comment: FD is usually diagnosed according to the Rome III criteria, and most clinical trials using any drugs such as acid suppressants and prokinetics are often performed after clinical subclassification according to the Rome III criteria. Therefore, treatment of FD based on its subtypes as described in the Rome III criteria may be appropriate, even though earlier reports indicate some controversy over the clinical significance of such subtype classification. A previous study suggested that the effect of FD treatment was decreased with increasing duration of dyspeptic symptoms [74], while another study reported no correlation between the effects of FD treatment and duration of dyspeptic symptoms [14]. Clearly consensus has not yet been achieved regarding the relationship between effects of FD treatment and duration of symptoms.

The guidelines for FD in both the Asia–Pacific region and the USA recommend changing to a different drug if adequate therapeutic efficacy has not been achieved after 4 weeks of treatment [75, 76]. And around 70 % of clinical trials in patients with FD have used 4 weeks as the period for evaluating therapeutic efficacy of the drug [75]. The Design of Treatment Trials Committee of the European Medicines Agency (EMEA) has approved a 4-week treatment period for evaluating the therapeutic efficacy of a drug in patients with functional gastrointestinal disorders [50]. Cessation of drug treatment may be associated with recurrence of symptoms at various rates [14, 77, 78]. However, there have been no reports of disadvantages due to the cessation of drug treatment after symptom resolution. Therefore, it may be sufficient to restart drug treatment after the recurrence of symptoms.

Prognosis and complications

- FD may be recurrent.
- FD may be associated with mood disturbances or neurotic disorders.
- The prevalence of overlap between FD and gastroesophageal reflux disease (GERD) is relatively high.
- The prevalence of overlap between FD and irritable bowel syndrome (IBS) is relatively high.
- The concurrence of FD and chronic constipation may be high.
- Chronic pancreatitis may not be completely excluded in patients with FD.

Comment: There are reports indicating the recurrence of FD. Three months after 4-week PPI treatment, approximately 20 % of treated FD patients had a recurrence [14]. Similarly, 6 months after *H. pylori* eradication, approximately 27 % of the treated FD patients had a recurrence [79].

Some previous studies have suggested that psychological problems are more commonly seen in FD patients than in patients with peptic ulcer disease and healthy controls [80, 81], but another study indicates that psychological problems in FD patients occurred at the same frequency as in healthy individuals [82]. A meta-analysis based on studies that were performed up to 2001 suggested that there was no significant difference in the ratios of affective disorders and neurotic disorders between FD patients and healthy individuals [23]. However studies that were published after the meta-analysis have led to the above statement, i.e., that FD may be associated with mood disturbance or neurotic disorders [83, 84]. In addition, be careful not to diagnose patients suffering from depression and somatization disorder as FD, because such patients sometimes complain of symptoms similar to digestive symptoms without reporting symptoms of depression and somatization disorder.

There are reports showing the prevalence of overlap between FD and GERD. According to those reports, 25 % of FD patients also show GERD symptoms [9]. Thus, such overlap will almost certainly be encountered by physicians in a clinical setting. There are also reports of prevalence overlap between FD and IBS. According to those reports, overall 30–60 % of FD patients also experience IBS [85]. That overlap will also be encountered in a clinical setting, in particular by physicians who act as consultants for FD patients.

Constipation, of undefined duration, was more prevalent in patients with FD than in patients with GERD and organic upper gastrointestinal disease [86], although there are no reports showing a correlation between FD and chronic constipation.

A subset of dyspeptic patients has reduced pancreatic function; one report suggests that chronic pancreatitis may be present in 24.1 % (111/460) of dyspeptic patients without a previous diagnosis of chronic pancreatitis [87]. No reports are available regarding the relationship between

FD and functional gallbladder and sphincter of Oddi disorders, or between FD and pancreatic cancer.

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Appendix

Members of the Working Committee who created and evaluated the JSGE "Evidence-based clinical guidelines for functional dyspepsia" are listed below.

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References

1. Tack J, Talley NJ, Camilleri M, et al. Functional gastroduodenal disorders. Gastroenterology. 2006;130:1466–79.
2. Kinoshita Y, Chiba T. Characteristics of Japanese patients with chronic gastritis and comparison with functional dyspepsia defined by ROME III criteria: based on the large-scale survey, FUTURE study. Intern Med. 2011;50:2269–76.
3. Manabe N, Haruma K, Hata J, et al. Clinical characteristics of Japanese dyspeptic patients: is the Rome III classification applicable? Scand J Gastroenterol. 2010;45:567–72.
4. Kinoshita K. Epidemiology of non-ulcer dyspepsia (NUD) in Japan. Nihon Shokakibyo Gakkai Zasshi. 1992;89:1973–81.
5. Schlemper RJ, van der Werf SD, Vandenbroucke JP, et al. Peptic ulcer, non-ulcer dyspepsia and irritable bowel syndrome in the Netherlands and Japan. Scand J Gastroenterol Suppl. 1993;200:33–41.
6. Hirakawa K, Adachi K, Amano K, et al. Prevalence of non-ulcer dyspepsia in the Japanese population. J Gastroenterol Hepatol. 1999;14:1083–7.
7. Kawamura A, Adachi K, Katsube T. Relationship between the prevalence of NUD and Helicobacter pylori infection. Ther Res. 2000;21:1341–3.
8. Kawamura A, Adachi K, Takashima T, et al. Prevalence of functional dyspepsia and its relationship with Helicobacter pylori infection in a Japanese population. J Gastroenterol Hepatol. 2001;16:384–8.
9. Kaji M, Fujiwara Y, Shiba M, et al. Prevalence of overlaps between GERD, FD and IBS and impact on health-related quality of life. J Gastroenterol Hepatol. 2010;25:1151–6.

10. Okumura T, Tanno S, Ohhira M. Prevalence of functional dyspepsia in an outpatient clinic with primary care physicians in Japan. J Gastroenterol. 2010;45:187–94.
11. Mahadeva S, Goh KL. Epidemiology of functional dyspepsia: a global perspective. World J Gastroenterol. 2006;12:2661–6.
12. Olafsdottir LB, Gudjonsson H, Jonsdottir HH, et al. Natural history of functional dyspepsia: a 10-year population-based study. Digestion. 2010;81:53–61.
13. Stanghellini V. Three-month prevalence rates of gastrointestinal symptoms and the influence of demographic factors: results from the Domestic/International Gastroenterology Surveillance Study (DIGEST). Scand J Gastroenterol Suppl. 1999;231:20–8.
14. Meineche-Schmidt V, Talley NJ, Pap A, et al. Impact of functional dyspepsia on quality of life and health care consumption after cessation of antisecretory treatment. A multicentre 3-month follow-up study. Scand J Gastroenterol. 1999;34:566–74.
15. Aro P, Talley NJ, Agreus L, et al. Functional dyspepsia impairs quality of life in the adult population. Aliment Pharmacol Ther. 2011;33:1215–24.
16. Haag S, Senf W, Hauser W, et al. Impairment of health-related quality of life in functional dyspepsia and chronic liver disease: the influence of depression and anxiety. Aliment Pharmacol Ther. 2008;27:561–71.
17. Gutiérrez A, Rodrigo L, Riestra S. Quality of life in patients with functional dyspepsia: a prospective 1-year follow-up study in Spanish patients. J Gastroenterol Hepatol. 2003;15:1175–81.
18. Kusunoki H, Haruma K, Manabe N. Therapeutic efficacy of acotiamide in patients with functional dyspepsia based on enhanced postprandial gastric accommodation and emptying: randomized controlled study evaluation by real-time ultrasonography. Neurogastroenterol Motil. 2012;24:540–5.
19. Quartero AO, de Wit NJ, Lodder AC, et al. Disturbed solid-phase gastric emptying in functional dyspepsia: a meta-analysis. Dig Dis Sci. 1998;43:2028–33.
20. Lunding JA, Tefera S, Gilja OH, et al. Rapid initial gastric emptying and hypersensitivity to gastric filling in functional dyspepsia: effects of duodenal lipids. Scand J Gastroenterol. 2006;41:1028–36.
21. Lemann M, Dederding JP, Flourie B, et al. Abnormal perception of visceral pain in response to gastric distension in chronic idiopathic dyspepsia. The irritable stomach syndrome. Dig Dis Sci. 1991;36:1249–54.
22. Samsom M, Verhagen MA, vanBerge Henegouwen GP, et al. Abnormal clearance of exogenous acid and increased acid sensitivity of the proximal duodenum in dyspeptic patients. Gastroenterology. 1999;116:515–20.
23. Henningsen P, Zimmermann T, Sattel H. Medically unexplained physical symptoms, anxiety, and depression: a metaanalytic review. Phychosom Med. 2003;65:528–33.
24. Haug TT, Mykletun A, Dahl AA. Are anxiety and depression related to gastrointestinal symptoms in the general population? J Gastroenterol. 2002;37:294–8.
25. Moayyedi P, Soo S, Deeks J, et al. Pharmacological interventions for non-ulcer dyspepsia. Cochrane Database Syst Rev. 2006;CD001960.
26. Miwa H, Nakajima K, Yamaguchi K, et al. Generation of dyspeptic symptoms by direct acid infusion into the stomach of healthy Japanese subjects. Aliment Pharmacol Ther. 2007;26:257–64.
27. Lee KJ, Kim JH, Cho SW. Dyspeptic symptoms associated with hypersensitivity to gastric distension induced by duodenal acidification. J Gastroenterol Hepatol. 2006;21:515–20.
28. Moayyedi P, Soo S, Deeks J, et al. Eradication of Helicobacter pylori for non-ulcer dyspepsia. Cochrane Database Syst Rev. 2006;CD002096.
29. Sugano K. Should we still subcategorize helicobacter pylori-associated dyspepsia as functional disease? J Neurogastroenterol Motil. 2011;17:366–71.
30. Locke GR 3rd, Zinsmeister AR, Talley NJ, et al. Familial association in adults with functional gastrointestinal disorders. Mayo Clin Proc. 2000;75:907–12.
31. Holtmann G, Siffert W, Haag S, et al. G-protein beta 3 subunit 825 CC genotype is associated with unexplained (functional) dyspepsia. Gastroenterology. 2004;126:971–9.
32. Mearin F, Perez-Oliveras M, Perello A, et al. Dyspepsia and irritable bowel syndrome after a Salmonella gastroenteritis outbreak: one-year follow-up cohort study. Gastroenterology. 2005;129:98–104.
33. Futagami S, Shindo T, Kawagoe T, et al. Migration of eosinophils and CCR2-/CD68-double positive cells into the duodenal mucosa of patients with postinfectious functional dyspepsia. Am J Gastroenterol. 2010;105:1835–42.
34. Tack J, Demedts I, Dehondt G, et al. Clinical and pathophysiological characteristics of acute-onset functional dyspepsia. Gastroenterology. 2002;122:1738–47.
35. Hongo M. Epidemiology of FGID symptoms in Japanese general population with reference to life style. J Gastroenterol Hepatol. 2011;26(Suppl 3):19–22.
36. Miwa H. Life style in persons with functional gastrointestinal disorders–large-scale internet survey of lifestyle in Japan. Neurogastroenterol Motil. 2012;24(464–71):e217.
37. Pilichiewicz AN, Feltrin KL, Horowitz M, et al. Functional dyspepsia is associated with a greater symptomatic response to fat but not carbohydrate, increased fasting and postprandial CCK, and diminished PYY. Am J Gastroenterol. 2008;103:2613–23.
38. Bortolotti M, Coccia G, Grossi G, et al. The treatment of functional dyspepsia with red pepper. Aliment Pharmacol Ther. 2002;16:1075–82.
39. Kusano M, Hosaka H, Moki H, et al. Cascade stomach is associated with upper gastrointestinal symptoms: a population-based study. Neurogastroenterol Motil. 2012;24(451–5):e214.
40. Lundquist P, Seensalu R, Linden B, et al. Symptom criteria do not distinguish between functional and organic dyspepsia. Eur J Surg. 1998;164:345–52.
41. Lorend M, Bucceri A, Catalano F. Pattern of gastric emptying in functional dyspepsia: an ultrasonographic study. Dig Dis Sci. 2004;49:404–7.
42. Misiara GP, Troncon LE, Moraes ER, et al. Comparison between manual and automated techniques for assessment of data from dynamic antral scintigraphy. Ann Nucl Med. 2008;22:761–7.
43. Holtmann G, Talley N. Hypothesis driven research and molecular mechanisms in functional dyspepsia: the beginning of a beautiful friendship in research and practice? J Gastroenterol. 2006;101:593–5.
44. Dimenas E, Glise H, Hallerback B. Portuguese validation of the Rome III diagnostic questionnaire for functional dyspepsia. Arq Gastroenterol. 2010;47:354–60.
45. Kakuta E, Yamashita N, Katsube T, et al. Abdominal symptom-related QOL in individuals visiting an outpatient clinic and those attending an annual health check. Intern Med. 2011;50:1517–22.
46. Hammer J, Eslick GD, Howell SC, et al. Diagnostic yield of alarm features in irritable bowel syndrome and functional dyspepsia. Gut. 2004;53:666–72.
47. Straus WL, Ofman JJ, MacLean C, et al. Do NSAIDs cause dyspepsia? A meta-analysis evaluating alternative dyspepsia definitions. Am J Gastroenterol. 2002;97:1951–8.
48. Holtmann G, Kutscher SU, Haag S, et al. Clinical presentation and personality factors are predictors of the response to treatment in patients with functional dyspepsia; a randomized, double-blind placebo-controlled crossover study. Dig Dis Sci. 2004;49:672–9.

49. de la Loge C, Trudeau E, Marquis P, et al. Cross-cultural development and validation of a patient self-administered questionnaire to assess quality of life in upper gastrointestinal disorders: the PAGI-QOL. Qual Life Res. 2004;13:1751–62.
50. Irvine EJ, Whitehead WE, et al. Design of treatment trials for functional gastrointestinal disorders. Gastroenterology. 2006;130:1538–51.
51. Vakil N, Laine L, Talley NJ, et al. Tegaserod treatment for dysmotility-like functional dyspepsia: results of two randomized, controlled trials. Am J Gastroenterol. 2008;103:1906–19.
52. Su C, Lichtenstein GR, Krok K, et al. A meta-analysis of the placebo rates of remission and response in clinical trials of active Crohn's disease. Gastroenterology. 2004;126:1257–69.
53. Ilnyckyj A, Shanahan F, Anton PA, et al. Quantification of the placebo response in ulcerative colitis. Gastroenterology. 1997;112:1854–8.
54. Talley NJ, Locke GR, Lahr BD, et al. Predictors of the placebo response in functional dyspepsia. Aliment Pharmacol Ther. 2006;23:923–36.
55. Enck P, Vinson B, Malfertheiner P, et al. The placebo response in functional dyspepsia—reanalysis of trial data. Neurogastroenterol Motil. 2009;21:370–7.
56. Francis C, Rona L, Laurence A. Psychosocial aspects of functional gastrointestinal disorders. In: Douglas AD (ed). Rome III the functional gastrointestinal disorders. Degnon Associates, McLean, 2006. p. 295.
57. Drossman DA. Psychosocial sound bites: exercises in the patient-doctor relationship. Am J Gastroenterol. 1997;92:1418–23.
58. Matsueda K, Hongo M, Tack J, et al. A placebo-controlled trial of acotiamide for meal-related symptoms of functional dyspepsia. Gut. 2012;61:821–8.
59. Mazzoleni LE, Sander GB, Francesconi CF, et al. *Helicobacter pylori* eradication in functional dyspepsia: HEROES trial. Arch Intern Med. 2011;171:1929–36.
60. Lan L, Yu J, Chen YL, et al. Symptom-based tendencies of *Helicobacter pylori* eradication in patients with functional dyspepsia. World J Gastroenterol. 2011;17:3242–7.
61. Moayyedi P. *Helicobacter pylori* eradication for functional dyspepsia: what are we treating?: comment on "*Helicobacter pylori* eradication in functional dyspepsia". Arch Intern Med. 2011;171:1936–7.
62. Tominaga K, Arakawa T. Kampo medicines for gastrointestinal tract disorders: a review of basic science and clinical evidence and their future application. J Gastroenterol. 2013;48:452–62.
63. Miwa H, Nagahara A, Tominaga K, et al. Efficacy of the 5-HT1A agonist tandospirone citrate in improving symptoms of patients with functional dyspepsia: a randomized controlled trial. Am J Gastroenterol. 2009;104:2779–87.
64. Passos Mdo C, Duro D, Fregni F. CNS or classic drugs for the treatment of pain in functional dyspepsia? A systematic review and meta-analysis of the literature. Pain Physician. 2008;11:597–609.
65. Hojo M, Miwa H, Yokoyama T, et al. Treatment of functional dyspepsia with antianxiety or antidepressive agents: systematic review. J Gastroenterol. 2005;40:1036–42.
66. Talley NJ, Riff DS, Schwartz H, et al. Double-blind placebo-controlled multicentre studies of rebamipide, a gastroprotective drug, in the treatment of functional dyspepsia with or without *Helicobacter pylori* infection. Aliment Pharmacol Ther. 2001;15:1603–11.
67. Miwa H, Osada T, Nagahara A, et al. Effect of a gastro-protective agent, rebamipide, on symptom improvement in patients with functional dyspepsia: a double-blind placebo-controlled study in Japan. J Gastroenterol Hepatol. 2006;21:1826–31.
68. Haug TT, Wilhelmsen I, Svebak S, et al. Psychotherapy in functional dyspepsia. J Psychosom Res. 1994;38:735–44.
69. Muth ER, Koch KL, Stern RM. Significance of autonomic nervous system activity in functional dyspepsia. Dig Dis Sci. 2000;45:854–63.
70. Lorena SL, Figueiredo MJ, Almeida JR, et al. Autonomic function in patients with functional dyspepsia assessed by 24-hour heart rate variability. Dig Dis Sci. 2002;47:27–31.
71. Calvert EL, Houghton LA, Cooper P, et al. Long-term improvement in functional dyspepsia using hypnotherapy. Gastroenterology. 2002;123:1778–85.
72. Liu S, Peng S, Hou X, et al. Transcutaneous electroacupuncture improves dyspeptic symptoms and increases high frequency heart rate variability in patients with functional dyspepsia. Neurogastroenterol Motil. 2008;20:1204–11.
73. Park YC, Kang W, Choi SM, et al. Evaluation of manual acupuncture at classical and nondefined points for treatment of functional dyspepsia: a randomized-controlled trial. J Altern Complement Med. 2009;15:879–84.
74. Bolling-Sternevald E, Lauritsen K, Talley NJ, et al. Is it possible to predict treatment response to a proton pump inhibitor in functional dyspepsia? Aliment Pharmacol Ther. 2003;18:117–24.
75. Talley NJ, Lam SK, Goh KL, et al. Management guidelines for uninvestigated and functional dyspepsia in the Asia-Pacific region: first Asian Pacific working party on functional dyspepsia. J Gastroenterol Hepatol. 1998;13:335–53.
76. Talley NJ, Vakil N. Guidelines for the management of dyspepsia. Am J Gastroenterol. 2005;100:2324–37.
77. Frazzoni M, Lonardo A, Grisendi A, et al. Are routine duodenal and antral biopsies useful in the management of "functional" dyspepsia? A diagnostic and therapeutic study. J Clin Gastroenterol. 1993;17:101–8.
78. Bjornsson E, Abrahamsson H, Simren M, et al. Discontinuation of proton pump inhibitors in patients on long-term therapy: a double-blind, placebo-controlled trial. Aliment Pharmacol Ther. 2006;24:945–54.
79. Maconi G, Sainaghi M, Molteni M, et al. Predictors of long-term outcome of functional dyspepsia and duodenal ulcer after successful *Helicobacter pylori* eradication—a 7-year follow-up study. Eur J Gastroenterol Hepatol. 2009;21:387–93.
80. Kok LP, Yap IL, Guan RY. Psychosocial aspects of non-ulcer dyspepsia. Singap Med J. 1989;30:346–9.
81. Nakao H, Konishi H, Mitsufuji S, et al. Comparison of clinical features and patient background in functional dyspepsia and peptic ulcer. Dig Dis Sci. 2007;52:2152–8.
82. Kaneko H, Mitsuma T, Fujii S, et al. Immunoreactive-somatostatin concentrations of the human stomach and mood state in patients with functional dyspepsia: a preliminary case-control study. J Gastroenterol Hepatol. 1993;8:322–7.
83. Pajala M, Heikkinen M, Hintikka J. Mental distress in patients with functional or organic dyspepsia: a comparative study with a sample of the general population. Aliment Pharmacol Ther. 2005;21:277–81.
84. Sattar A, Salih M, Jafri W. Burden of common mental disorders in patients with functional dyspepsia. J Pak Med Assoc. 2010;60:995–7.
85. Lee HJ, Lee SY, Kim JH, et al. Depressive mood and quality of life in functional gastrointestinal disorders: differences between functional dyspepsia, irritable bowel syndrome and overlap syndrome. Gen Hosp Psychiatry. 2010;32:499–502.
86. Hammer J, Talley NJ. Disturbed bowel habits in patients with non-ulcer dyspepsia. Aliment Pharmacol Ther. 2006;24:405–10.
87. Andersen BN, Scheel J, Rune SJ, et al. Exocrine pancreatic function in patients with dyspepsia. Hepatogastroenterology. 1982;29:35–7.

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Kyoto global consensus report on *Helicobacter pylori* gastritis

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ABSTRACT

Objective To present results of the Kyoto Global Consensus Meeting, which was convened to develop global consensus on (1) classification of chronic gastritis and duodenitis, (2) clinical distinction of dyspepsia caused by *Helicobacter pylori* from functional dyspepsia, (3) appropriate diagnostic assessment of gastritis and (4) when, whom and how to treat *H. pylori* gastritis.

Design Twenty-three clinical questions addressing the above-mentioned four domains were drafted for which expert panels were asked to formulate relevant statements. A Delphi method using an anonymous electronic system was adopted to develop the consensus, the level of which was predefined as ≥80%. Final modifications of clinical questions and consensus were achieved at the face-to-face meeting in Kyoto.

Results All 24 statements for 22 clinical questions after extensive modifications and omission of one clinical question were achieved with a consensus level of >80%. To better organise classification of gastritis and duodenitis based on aetiology, a new classification of gastritis and duodenitis is recommended for the 11th international classification. A new category of *H. pylori*-associated dyspepsia together with a diagnostic algorithm was proposed. The adoption of grading systems for gastric cancer risk stratification, and modern image-enhancing endoscopy for the diagnosis of gastritis, were recommended. Treatment to eradicate *H. pylori* infection before preneoplastic changes develop, if feasible, was recommended to minimise the risk of more serious complications of the infection.

Conclusions A global consensus for gastritis was developed for the first time, which will be the basis for an international classification system and for further research on the subject.

INTRODUCTION

For decades endoscopic 'gastritis,' gastric erosions and even histological findings of gastric inflammation have failed to attract much attention from clinicians as the majority of patients with these findings remain asymptomatic. Although gastritis is often used to describe dyspeptic symptoms, the presence of such symptoms correlates poorly with histological or endoscopic gastritis. Although the term 'gastritis' is still used as a concept to explain dyspeptic symptoms, gastritis as a term refers to gastric inflammation, often accompanying structural mucosal changes.[1] This gastric inflammation (gastritis) has long been associated with peptic ulcer, gastric cancer and pernicious anaemia, but the cause or causes of gastritis remain poorly understood. The discovery that *Helicobacter pylori* (*H. pylori*) was a cause of gastritis[2] focused attention on the aetiology, natural history and prognosis of gastritis.

Worldwide the most common cause of chronic gastritis is infection with *H. pylori*. *H. pylori* causes progressive damage to the gastric mucosa and is now accepted as playing a causative role in a number of important diseases, including duodenal ulcer disease, gastric ulcer disease, gastric adenocarcinoma and gastric mucosa-associated lymphoid tissue (MALT) lymphoma.[3–5] Indeed, *H. pylori*–induced gastritis is considered as the most important risk factor for peptic ulcer and its complications as well as for gastric cancer.[5]

The current International Statistical Classification of Diseases and Related Health Problems (ICD-10), issued in 1989 by the International Conference for the Tenth Revision of the ICD was endorsed by WHO at the 43rd general assembly in 1990 and has been used for disease statistics since 1994 among member countries of WHO. In the ICD-10, all the digestive diseases are classified under K code with different two-digit numbers.[6] However, *H. pylori* was not integrated into gastritis classification in the gastritis section (K29) of ICD-10, even though *H. pylori* gastritis is the predominant type of gastritis and clinically by far the most relevant because of its predisposing role of severe gastroduodenal complications.[3–5] Moreover, the current ICD-10 classification of gastritis is not organised according to aetiology but is merely a mixture of phenotype and aetiology and also includes duodenitis (box 1). Therefore, a revision of the gastritis and duodenitis classification based on all the possible aetiologies was proposed after the working group meeting for the ICD-11 revision held in Tokyo in 2010 and submitted as the ICD11 β foundation component. However, in the ICD11 β foundation classification (box 2), the original plan was changed. In an attempt to gather broader opinions on the rationale of the new classification system originally proposed to ICD-11, we devoted one section to this important issue at this meeting.

As stated above, if *H. pylori* gastritis is categorised as an infectious disease, the inclusion of *H. pylori* gastritis-associated dyspeptic symptoms as a 'functional disease' entity poses a special challenge,[7 8] despite it being implicated in the pathogenesis of functional dyspepsia (FD) symptoms.[9] Despite the definition given by Rome III,[9] a conceptual ambiguity on how to deal with *H. pylori* gastritis-associated

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Box 1 Current International Statistical Classification of Diseases and Related Health Problems (ICD-10) classification of gastritis (K29 code) http://apps.who.int/classifications/icd10/browse/2015/en#/K29

K29 Gastritis and duodenitis
Excl: eosinophilic gastritis or gastroenteritis (K52.8)
Zollinger–Ellison syndrome (E16.4)
K29.0 Acute haemorrhagic gastritis
Incl: Acute (erosive) gastritis with haemorrhage
Excl: erosion (acute) of stomach (K25.–)
K29.1 Other acute gastritis
K29.2 Alcoholic gastritis
K29.3 Chronic superficial gastritis
K29.4 Chronic atrophic gastritis
Incl: Gastric atrophy
K29.5 Chronic gastritis, unspecified
Incl: Chronic gastritis
Antral
Fundal
K29.6 Other gastritis
Incl: Giant hypertrophic gastritis
Granulomatous gastritis
Ménétrier disease
K29.7 Gastritis, unspecified
K29.8 Duodenitis
K29.9 Gastroduodenitis, unspecified

Excl, exclusion criteria; Incl, inclusion criteria.

dyspeptic symptoms in the context of the clinical assessment of FD still remains.[5 10–12] Accordingly, guidelines and meta-analyses that included dyspepsia associated with *H. pylori* under the umbrella of 'functional dyspepsia'[5 10–12] would require reconsideration in accordance with advances made in the area of *H. pylori* gastritis.

Third, there has been significant technical progress in diagnostic tools for GI diseases. Advanced endoscopy with image-enhanced modalities and magnification allows diagnosis of gastritis with a high degree of accuracy, even before histological confirmation.[13–15] Furthermore, non-invasive diagnostic tests such as the [^{13}C]-urea breath test, faecal antigen test and serological parameters serve as surrogate markers of *H. pylori* gastritis and indicators of gastritis severity.[5] Classification systems for grading gastritis such as the Operative Link for Gastritis Assessment (OLGA) and Operative Link for Gastric Intestinal Metaplasia Assessment (OLGIM) have also been proposed,[16–18] in addition to the internationally accepted Sydney System,[19 20] and their utility needs to be evaluated and agreed upon.

In 2013, the Japanese government insurance policy approved eradication therapy for *H. pylori*-positive gastritis after endoscopic examination, to exclude more serious diseases such as ulcer and cancer, in line with the Japanese guidelines for *H. pylori* management.[11] However, no global consensus has been published on when to recommend eradication therapy for *H. pylori* gastritis and how to follow up after eradication.

Since the global awareness of gastritis is still confounded by a number of controversial issues as described above, a meeting was set up in Kyoto to achieve global consensus on *H. pylori* gastritis; to attempt conceptual changes in gastritis classification in general; to agree diagnosis and management strategies with special reference to FD and cancer prevention.

METHOD

Consensus development process

Four major topics were chosen by core members of the organising committee (KS, NU and PM). Drafts of clinical questions (CQs) about each topic were prepared by the ad hoc committee of the Japanese Society of Gastroenterology (JSGE) and were further revised by core members (KS, PM and EME-O). Altogether, 23 CQs were selected for the first round of voting.

Faculty members were selected from members of the JSGE, European Helicobacter Study Group, Asian Pacific Association of Gastroenterology, Healthy Stomach Initiative and the working group members of gastroenterology for ICD-11. These members were assigned to one of the four subgroups by core members (KS, NU and PM) based on their expertise and two members from each subgroup were invited to serve as moderators. The faculty members of each group were assigned one or two CQs for which they were asked to prepare statements and supporting evidence. These statements were edited by moderators and core members and uploaded to the electronic voting system developed by JSGE.

The Delphi method was used for consensus development, and voting by each faculty member was done anonymously through the electronic system. Each faculty member was asked to indicate one of the following levels of agreement: strongly agree, agree with minor reservation, agree with major reservation, disagree with minor reservation, disagree with major reservation and strongly disagree. If the member's vote was other than strongly agree or agree with minor reservation, they were asked to give the reasons for reservation or disagreement.

Consensus level was predefined as ≥80% of the sum of the votes of strongly agree plus agree with minor reservation. After the first round of voting, moderators in each subgroup initiated further discussion about the statements which had failed to reach consensus. After this discussion, the revised statements were uploaded to the electronic voting system for a second round of voting. This process resulted in several CQs being modified for improved understanding and to better fit the statements. At the second round of voting, faculty members were asked to provide recommendation as to the grade of evidence and the levels of supporting evidence for the statements. Recommendation grade and evidence level were based on the GRADE system[21 22] (see online supplementary table S1 and S2). Electronic reminders were automatically sent to all faculty members twice (3 days and 1 day before the closing dates). Voting rates of 100% were achieved in the two voting sessions.

The second round of voting was followed by a face-to-face meeting in Kyoto on 31 January to 1 February 2014. On the first day, preliminary plenary voting was conducted since faculty members had hitherto been blinded to the voting results in other sections. This process identified several statements which failed to achieve consensus of ≥80%. Each group then met to resolve disagreements and better reflect opinions from all group members. On the second day, the revised statements were presented at plenary discussions with all group members. Voting for each statement was done using a key pad system with the levels of agreements being shown on the screen in real time. Statements that failed to reach consensus were discussed, revised if considered necessary and voted on again. Finalised statements were summarised by moderators assigned to each group.

The five colleagues who could not attend the face-to-face meeting or missed the final voting were invited later to give

Box 2 Classification of gastritis (2A) and duodenitis (2B) in the foundation component of International Statistical Classification of Diseases and Related Health Problems (ICD11 β) (as accessed at 20 January 2015) http://apps.who.int/classifications/icd11/browse/f/en#/

Please note that this classification is continuously updated and hence is subject to change. This classification is not authorised by WHO.

2A Classification of gastritis at the foundation layer of ICD11 β

Helicobacter pylori-induced gastritis
Drug-induced gastritis
Autoimmune gastritis
Stress-induced gastritis
Special forms of gastritis
- Allergic gastritis
- Gastritis due to biliary reflux
- Lymphocytic gastritis
- Ménétrier disease
- Eosinophilic gastritis

Infectious gastritis
- Gastric phlegmone
- Bacterial gastritis
  - *H. pylori*-induced gastritis
  - Enterococcal gastritis
  - Mycobacterial gastritis
    - Tuberculous gastritis
    - Non-tuberculous mycobacterial gastritis
      - *Mycobacterium avium*-intracellulare gastritis
      - Gastritis due to other specified non-tuberculous mycobacteria
    - Secondary syphilitic gastritis
- Viral gastritis
  - Cytomegaloviral gastritis
  - Enteroviral gastritis
- Fungal gastritis
  - Gastritis due to mucoromycosis
  - Gastric candidiasis
  - Gastric histoplasmosis
- Parasitic gastritis
  - Gastric anisakiasis
  - Cryptosporidium gastritis
  - Gastric *strongyloides stercoralis*

Gastritis due to other diseases classified elsewhere
- Gastritis due to Crohn's disease
- Gastritis due to sarcoidosis
- Gastritis due to vasculitis

Gastritis due to external causes
- Alcoholic gastritis
- Radiation gastritis
- Chemical gastritis
- Gastritis due to other specified external causes

Gastritis of unknown aetiology with specific endoscopic or pathological features
- Superficial gastritis
  - Acute superficial gastritis
  - Chronic superficial gastritis
- Acute haemorrhagic gastritis
- Chronic atrophic gastritis
  - Mild to moderate gastric atrophy
  - Severe gastric atrophy
- Metaplastic gastritis
- Granulomatous gastritis
- Hypertrophic gastritis

Other gastritis
- Chronic gastritis, not elsewhere classified
- Acute gastritis, not elsewhere classified

2B Classification of duodenitis at the foundation layer

Helicobacter pylori-induced duodenitis
Stress-induced duodenitis
Duodenitis due to external causes
- Alcoholic duodenitis
- Chemical duodenitis
- Radiation duodenitis
- Duodenitis due to other external causes
- Drug-induced duodenitis

Special forms of duodenitis
- Allergic duodenitis
- Eosinophilic duodenitis
- Lymphocytic duodenitis

Infectious duodenitis
- Duodenal phlegmone
- Bacterial duodenitis
  - Mycobacterial duodenitis
    - Non-tuberculous mycobacterial duodenitis
    - Tuberculous duodenitis
  - Duodenitis due to Whipple's disease
- Fungal duodenitis
  - Duodenal candidiasis
- Parasitic duodenitis
  - Ancylostomiasis duodenitis
  - Duodenal anisakiasis
  - Duodenitis due to *Giardia lamblia*
  - Strongyloides duodenitis
- Viral duodenitis
  - Cytomegaloviral duodenitis
  - Herpetic duodenitis

Duodenitis due to other diseases, classified elsewhere
- Duodenitis due to coeliac disease
- Duodenitis due to Crohn's disease
- Duodenitis due to sarcoidosis
- Duodenitis due to vasculitis
  - Duodenitis due to IgA vasculitis
- Duodenitis due to Whipple's disease

Duodenitis of unknown aetiology with specific endoscopic or pathological features
- Acute haemorrhagic duodenitis
- Granulomatous duodenitis

their votes for all the finalised statements without notification of the plenary voting results. The impact of their votes is discussed below.

For management of conflict of interest (COI), each member was asked to present COI status according to the JSGE guidelines. If a relevant COI had existed, that person would have been asked not to vote, in accordance with the recent consensus,[23] but no such case was encountered. The majority of the funding was provided by JSGE with a hand-reach support from industries, which were otherwise not involved in the planning, organisation or manuscript writing and did not join in the discussions.

Process and results

At the first round of voting 16 CQs achieved the predefined consensus level of ≥80%. Six statements failed to reach consensus and each section met to modify their assigned statements based on the comments and opinions received. This led to some questions being split into two or being combined, resulting in 24 CQs, including 25 statements which were subjected to the second round of voting within their assigned group. The results of the second round of voting were disclosed on the first day of the face-to-face meeting in Kyoto. At this stage, all statements except one had achieved consensus. To facilitate further discussion in the break-out sessions, preliminary plenary voting was done to enable the respective section members to consider the opinions of all group members.

On the second day, the finalised CQs and accompanying statements were presented for plenary voting. If consensus levels were not reached, open discussions ensued to modify the statements, followed by voting. All the finalised CQs and statements are shown in the four consensus sections. Levels of recommendation and evidence are shown together with the voting results. For CQ1 to CQ8A, 39 members voted, while 38 voted for CQ8B to CQ14A and 37 voted for CQ14B to CQ23. During the plenary voting, one subdivided CQ (CQ19) was recombined, while another CQ (CQ21) was deleted because of redundancy, resulting in 22 CQs and 24 statements. All voting during the plenary session was done anonymously by an electronic voting system with key pads distributed to each faculty member. The five faculty members who missed the plenary voting session were asked to vote later for the finalised CQs and statements without knowledge of the plenary voting results. Their voting results were almost identical with the plenary voting results. They agreed on all the CQs with the only exception being CQ11, showing 80% (one out of five) agreement. Since there was no inconsistency between the plenary voting and voting by the absentees, combining the two sets of results did not influence the outcome. The entire consensus results are shown below.

CONSENSUS STATEMENT

Section 1. Classification of gastritis in relation to ICD-11

CQ1. Is the current ICD-10 classification for gastritis appropriate?

Statement 1

The current ICD-10 classification for gastritis is obsolete in view of the discovery of *H. pylori*.

Grade of recommendation: strong
Evidence level: high
Consensus level: 100%

Comment

The ICD-10 classification of gastritis was formulated in 1989 and is still in effect in most countries. At the time of formulation, the ICD-10 classification of gastritis and duodenitis (K29) was rudimentary as it was based on macroscopic and histomorphological criteria; the only aetiological factor assigned was alcohol[6] (box 1). The histological classification of gastritis considered mainly aspects of atrophy and autoimmunity.[1]

The discovery of *H. pylori* had not been taken into account, possibly because even though release came after the discovery of *Campylobacter pylori* (*H. pylori*), the role of *H. pylori* in disease was still controversial. The recognition of *H. pylori* infection as the primary cause of chronic gastritis proved to be a breakthrough that reopened the chapter on gastritis and its role in disease.[2 24 25] At present, no classification of gastritis would be complete without including *H. pylori* as the aetiological cause.

CQ2. Is the proposed ICD-11 classification for gastritis appropriate?

Statement 2

The newly proposed classification of gastritis in the ICD11 β version is an improvement because it is based on aetiological factors.

Grade of recommendation: strong
Evidence level: moderate
Consensus level: 100%

Comment

Although the ICD-10 has been updated regularly to accommodate new diseases and concepts, WHO recognised the necessity of overall systematic changes in the ICD and decided to revise the current ICD-10 to ICD-11 in 2007. As the intermediate process for this revision, the ICD11 β version was formulated with input from various scientific advisory groups. This version was open to the public so that opinions from various interest groups and a broader range of medical specialists could be reflected before compiling the ICD-11. ICD11 β foundation component consists of the core of the ICD-11 classification from which mortality and morbidity classifications will derive. However, it remains a draft and can be changed from time to time before finalisation of ICD-11 (for more details, please visit http://www.who.int/classifications/icd/revision/betaexpectations/en/).

In the ICD11 β foundation component of the gastritis section, classification of gastritis was principally based on aetiological factors with consideration of their specific pathophysiological principles (box 2). Accordingly, *H. pylori* gastritis is categorised as a specific nosological entity.

The assessment of gastritis based on histopathological criteria was completely changed after recognition of *H. pylori* as the most common cause of chronic gastritis. The Sydney System was developed as a consequence and has been integrated into clinical practice. The Sydney classification of gastritis combined histological parameters of activity, chronicity, atrophy, intestinal metaplasia, topographical distribution and aetiopathogenic information for reporting the pathology of gastritis in endoscopic biopsies.[19 20]

As described above, classification of gastritis in the foundation component of ICD11 β version is principally based on causative factors, in order to cover the three most important and best defined categories of gastritis—namely, (a) *H. pylori*-induced, (b) drug-induced and (c) autoimmune gastritis. A specific diagnosis among these different categories of gastritis is required to direct specific management and treatment strategies. The diagnosis of *H. pylori*-induced gastritis has major implications for life-long healthcare. *H. pylori* gastritis may cause dyspeptic symptoms[26 27] and result in gastroduodenal pathologies, including peptic ulcer disease (PUD) and gastric cancer. The recognised role of *H. pylori* as a carcinogen makes eradication of *H. pylori* infection the preferred strategy for the prevention of gastric cancer.[5 11 28] There is more to learn about aetiologies other than *H. pylori* in gastritis and this is dealt with as '*H. pylori*-negative or idiopathic gastritis'.[29]

The proposed aetiology-based classification for gastritis in the foundation component of ICD11 β version was further refined by this consensus meeting (box 3). Clinical validation is needed to further define and confirm the usefulness of the new classification.

Furthermore, duodenitis, which was in the gastritis section in ICD-10, is now categorised in an independent section in the

Box 3 Aetiology-based classification of gastritis (3A) and duodenitis (3B). A proposal according to the consensus at the Kyoto consensus conference

3A Proposed classification of gastritis in the Kyoto consensus conference

Autoimmune gastritis

Infectious gastritis
- *Helicobacter pylori*-induced gastritis
- Bacterial gastritis other than *H. pylori*
  - *Helicobacter heilmannii* gastritis
  - Enterococcus gastritis
  - Mycobacteria gastritis
  - Secondary syphilitic gastritis
- Gastric phlegmone
- Viral gastritis
  - Enteroviral gastritis
  - Cytomegalovirus gastritis
- Fungal gastritis
  - Gastritis due to mucormycosis
  - Gastric candidiasis
  - Gastric histoplasmosis
- Parasitic gastritis
  - Cryptosporidium gastritis
  - Gastric *strongyloides stercorale*
  - Gastric anisakiasis

Gastritis due to external causes
- Drug-induced gastritis
- Alcoholic gastritis
- Radiation gastritis
- Chemical gastritis
- Gastritis due to duodenal reflux
- Gastritis due to other specified external cause

Gastritis due to specified causes
- Lymphocytic gastritis
- Ménétrier disease
- Allergic gastritis
- Eosinophilic gastritis

Gastritis due to other diseases classified elsewhere
- Gastritis due to sarcoidosis
- Gastritis due to vasculitis
- Gastritis due to Crohn's disease

3B Proposed classification of duodenitis in the Kyoto consensus conference

Infectious duodenitis
- *H. pylori*-induced duodenitis
- Bacterial duodenitis other than *H. pylori*
  - Mycobacterial duodenitis
  - Duodenitis due to *Tropheryma whipplei* (Whipple's disease)
- Duodenal phlegmone
- Fungal duodenitis
  - Duodenal candidiasis
- Parasitic duodenitis
  - Ancylostomasis (hookworm) duodenitis
  - Duodenal anisakiasis
  - Duodenitis due to *Giardia lamblia*
  - Strongyloides duodenitis
- Viral duodenitis
  - Cytomegaloviral duodenitis
  - Herpetic duodenitis

Duodenitis due to external causes
- Alcoholic duodenitis
- Chemical duodenitis
- Radiation duodenitis
- Duodenitis due to other external causes
- Drug-induced duodenitis

Duodenitis due to specified causes
- Allergic duodenitis
- Eosinophilic duodenitis
- Lymphocytic duodenitis

Duodenitis due to other diseases classified elsewhere
- Duodenitis due to Crohn's disease
- Duodenitis due to sarcoidosis
- Duodenitis due to vasculitis
- Duodenitis due to Henoch–Schönlein purpura
- Duodenitis due to coeliac disease

foundation component. It should be noted that the Joint Linearisation of Mortality and Morbidity of ICD11 β version is now publicly available (see online supplementary table S3) and differs significantly from the foundation component (box 2) or aetiology-based classification proposed in this paper (box 3). This linearisation did not adopt the principle of aetiology-based classification, thus requiring further revision.

CQ3. Is it necessary to categorise gastritis according to gastric subsite?

Statement 3

It is useful to categorise *H. pylori*-induced gastritis according to gastric subsites, because the risks of gastric cancer and peptic ulcer are affected by the patterns of gastritis.

Grade of recommendation: strong

Evidence level: high

Consensus level: 97.4%

Comment

The categorisation of *H. pylori* gastritis according to gastritis subsites together with the assessment of gastritis severity allows prediction of an individual's risk of developing severe gastroduodenal complications and, in particular, gastric cancer.[30–32]

Depending on the gastric subsites involved, gastric function and, in particular, gastric acid secretion may be profoundly affected, resulting in gastric acid hypersecretion, hyposecretion or even achlorhydria.[33–35]

Subsite characterisation of gastritis is also critically important for identifying those patients who remain at high risk after *H. pylori* eradication and thus are candidates for regular endoscopic and histological follow-up.[36] Patients with severe atrophic gastritis (with or without intestinal metaplasia) in the corpus or with severe corpus predominant gastritis are those at highest risk for progression to gastric cancer of the intestinal type[31 37] and for diffuse-type gastric cancer. In diffuse-type gastric cancer the prevalence of antral atrophic gastritis is almost identical to that seen in the intestinal type but is slightly less with corpus atrophic gastritis than with intestinal type gastric cancer.[38]

CQ4. Is it necessary to categorise gastritis according to histology (severity) and/or endoscopy?

Statement 4

It is advisable to categorise gastritis according to histology, because the risk of development of gastric cancer in *H. pylori*

gastritis varies according to the extent and severity of inflammation and atrophy.

Grade of recommendation: strong
Evidence level: high
Consensus level: 100%

Comment

The updated Sydney System has been globally implemented into clinical practice and requires proper assessment of all the relevant characteristics of *H. pylori* gastritis including atrophy and intestinal metaplasia at different gastric subsites.[19 20] Categorising gastritis is clinically relevant because the 'phenotype' of *H. pylori* gastritis determines the risk of progression to gastroduodenal complications.

Severity and extent of atrophic gastritis and intestinal metaplasia are well established as indicators of the increased risk for developing gastric cancer.[31 39 40] Similarly, severe *H. pylori*-induced corpus gastritis is associated with an increased risk for gastric cancer.[31 41] New staging systems for the characterisation of gastritis have been introduced to assess the gastric cancer risk. They are used in clinical practice and are either based on the severity of atrophy in various gastric subsites (OLGA)[16 17] or on intestinal metaplasia (OLGIM).[18] Both systems, discussed further in section 3, are reported to have a positive impact on patient management.

CQ5. How should we classify gastric erosions in the context of chronic gastritis?

Statement 5

Gastric erosions should be reported separately from gastritis. The natural history and clinical significance of gastroduodenal erosions depend on aetiology and need further clarification.

Grade of recommendation: strong
Evidence level: low
Consensus level: 100%

Comment

Gastric erosions are defined as superficial mucosal breaks with a diameter of $\leq$3 mm or <5 mm.[42] This small size makes it less likely to confound erosions with peptic ulcers which, by definition, penetrate the muscularis mucosae.[3]

Gastric erosions can be detected in the context of *H. pylori* infection but are more frequently caused by intake of mucosal damaging drugs—in particular, aspirin and non-steroidal anti-inflammatory drugs (NSAIDs).[43 44]

Furthermore, several different morphological forms were noted after eradication of *H. pylori* as (a) flat, (b) raised, (c) haemorrhagic and (d) appearing as bleeding spots with localisation in the antrum in the absence of drugs,[45] possibly owing to hyperacidity after eradication therapy.[46 47]

From a clinical perspective, the most relevant aspect of erosions is that patients taking NSAIDs and having numerous erosions in the stomach are at increased risk of developing ulcers subsequently.[48]

Few studies on the clinical significance or natural history of gastric or duodenal erosions have been reported. Thus, it is important to conduct a prospective research in which erosions in the stomach and duodenum are separately reported in conjunction with the category of gastritis, which is needed to better understand the natural history of gastric erosions and their potential to progress to ulceration and bleeding. Validated scores for reporting erosions for research purposes should be used.[49]

CQ6. Is *H. pylori* gastritis an infectious disease irrespective of symptom and complications?

Statement 6

H. pylori gastritis should be defined as an infectious disease, even when patients have no symptoms and irrespective of complications such as peptic ulcers and gastric cancer.

Grade of recommendation: strong
Evidence level: high
Consensus level: 100%

Comment

H. pylori gastritis is an infectious disease and leads to chronic active gastritis of varying severity in virtually all infected subjects.[50]

There is a significant variability in the interindividual expressions of gastric mucosal structural damage and accordingly the associated physiological perturbations also vary.[30 35] *H. pylori* gastritis may remain clinically unapparent or evolve into severe complications. The rate of progression is unpredictable. The most severe clinical expression is gastric cancer, which is often incurable by the time of diagnosis.

Cure of *H. pylori* infection leads to healing of the inflamed gastric mucosa, which may return to normal. *H. pylori* eradication may improve or resolve dyspeptic symptoms and usually cures PUD. *H. pylori* gastritis is a disease which can be cured and thus prevent severe complications. If *H. pylori* gastritis has progressed to more severe forms of gastritis, including atrophic gastritis with or without intestinal metaplasia, or severe corpus predominant gastritis, the risk of gastric cancer is increased and eradication of the infection at this stage needs to be integrated with a follow-up strategy.[5 11 28 31 36 40]

Section 2 Dyspepsia associated with *H. pylori* infection

CQ7. Does *H. pylori* gastritis cause dyspepsia?

Statement 7

H. pylori gastritis is the cause of dyspepsia in a subset of patients.

Grade of recommendation: strong
Evidence level: high
Consensus level: 100%

Comment

A large number of observations support the conclusion that *H. pylori* infection may be a cause of symptoms in a proportion of patients presenting with dyspepsia.[26 27] First, acute iatrogenic or self-administered infection with *H. pylori* can induce acute dyspeptic symptoms.[24 25] However, while persistent colonisation virtually always leads to chronic gastritis,[48] in the majority of individuals severe dyspeptic symptoms are transient.[24 25 51] Second, most but not all, epidemiological studies show associations between *H. pylori* infection and (uninvestigated) dyspeptic symptoms.[52–55] The most convincing evidence can be derived from *H. pylori* eradication studies in infected patients with uninvestigated or FD.[12 56–61] In these studies, eradication is associated with a small but statistically significant benefit for symptom control over no eradication; the estimated number needed to treat is 14[12] and in a more recent study the number was 8.[61] At present there are no criteria to predict whether a patient with dyspeptic symptoms will respond to eradication therapy or not. Therefore, the only way in clinical practice is to eradicate the *H. pylori* infection and see whether symptoms resolve or whether additional treatments will be required. The symptomatic gain takes at least 6 months to become significant over no eradication and this has been attributed to the time it takes for gastritis to recover.[12 59–61]

CQ8. Should we categorise *H. pylori*-associated dyspepsia as a specific entity?

Statement 8A

In *H. pylori*-infected patients with dyspepsia, symptoms can be attributed to *H. pylori* gastritis if successful eradication therapy is followed by sustained symptom remission.

Grade of recommendation: strong
Evidence level: high
Consensus level: 97.4%

Statement 8B

H. pylori-associated dyspepsia (as in statement 8A) is a distinct entity.

Grade of recommendation: strong
Evidence level: moderate
Consensus level: 92.1%

Comment

Based on the Rome III consensus,[9 62] FD is defined as "the presence of chronic dyspeptic symptoms (postprandial fullness, early satiation, epigastric pain or burning) without evidence of structural disease (including at upper endoscopy) that is likely to explain the symptoms" (figure 1). This group was contrasted with those in whom chronic dyspeptic symptoms have an identified organic or metabolic cause, where elimination of that cause or improvement of the disease leads to resolution or improvement of symptoms.[9]

The Rome III consensus mentions a subset of patients with *H. pylori* gastritis as representative of organic dyspepsia if they respond to eradication. Patients with *H. pylori* gastritis in whom symptoms persist despite eradication therapy eliminating the infection were identified as having FD.[9] As mentioned above, eradication therapy studies showed that a subset of *H. pylori*-infected patients with FD derive symptomatic benefit from eradication, with a delay of at least 6 months from cure of the infection.[12 59–61]

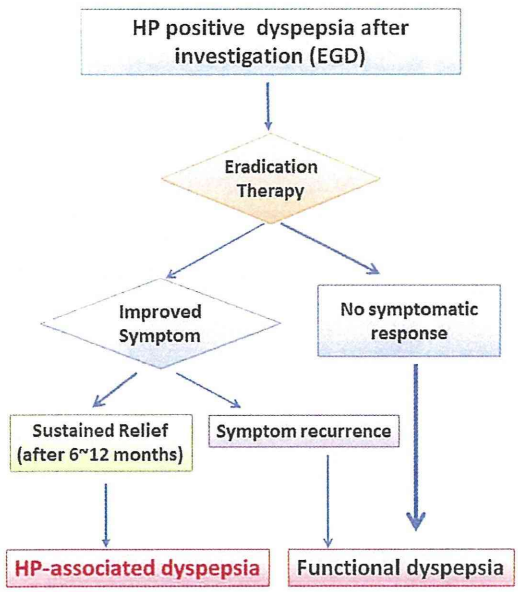

Figure 1 Diagnostic algorithm of *Helicobacter pylori*-associated dyspepsia. Patients with dyspeptic symptoms after negative routine laboratory and upper gastrointestinal endoscopy except for positive *H. pylori* tests, should undergo eradication therapy. If sustained symptomatic relief is obtained, their dyspeptic symptoms are considered as *H. pylori*-associated dyspepsia. On the other hand, if dyspeptic symptoms do not resolve or recur after eradication therapy, they are judged to have functional dyspepsia. EGD, oesophagastroduodenoscopy.

Based on these considerations, sustained symptom control after successful eradication identifies *H. pylori* as the organic cause of the symptoms in these patients and provides the rationale to consider *H. pylori*-associated dyspepsia as a separate clinical entity. *H. pylori*-infected patients with chronic dyspeptic symptoms and negative endoscopy are now treated and labelled depending on their treatment response as outlined in figure 1.

CQ9. Is eradication of *H. pylori* infection first-line treatment for improving dyspeptic symptoms?

Statement 9

Eradication of *H. pylori* is first-line treatment for *H. pylori*-infected dyspeptic patients.

Grade of recommendation: strong
Evidence level: high
Consensus level: 94.7%

Comment

As is apparent from statement 8, there is a group of patients with FD for whom *H. pylori* is considered the cause of their symptoms, and this can be established if eradication is associated with sustained symptom benefit.[9 59–61] This scenario is the only one where patients with chronic dyspeptic symptoms and a negative endoscopy can be 'cured', albeit with some delay after successful eradication therapy.[12 59–61] Moreover, very few effective alternative therapeutic approaches have been proved to have substantial and sustained benefit in FD.[63] Finally, eradication therapy is a short treatment, with acceptable cost–benefit for controlling dyspeptic symptoms, and with other potential benefits for prevention of peptic ulcer and gastric cancer.[5] Based on these considerations, eradication therapy can be proposed as first-line treatment for *H. pylori*-infected dyspeptic patients, which is in line with a recent management algorithm by the Rome foundation.[64]

CQ10. How effective is *H. pylori* eradication on dyspeptic symptoms—in the short and long term—and how does it compare with other treatments (such as proton pump inhibitors (PPIs))?

Statement 10

In *H. pylori*-infected dyspeptic patients, eradication therapy for dyspeptic symptoms is better than placebo and is the preferred option.

Grade of recommendation: strong
Evidence level: high
Consensus level: 97.4%

Comment

Eradication therapy studies have confirmed that a subset of *H. pylori*-infected patients with FD is relieved of dyspeptic symptoms by eradication therapy.[12 56–61] To date, only a limited number of studies have directly compared eradication therapy with other treatments that are used for FD, such as PPIs or prokinetic therapy.[57 60 61] Hence, although the symptomatic gain takes at least 6 months,[57 60 61] eradication is the preferred treatment. Future trials should compare eradication with treatment modalities other than placebo in *H pylori*-infected patients with chronic dyspeptic symptoms and a negative endoscopy.

CQ11. Should patients who remain dyspeptic after successful *H. pylori* eradication be considered to have FD?

Statement 11

Patients who remain symptomatic after successful *H. pylori* eradication should be considered to have FD.

Grade of recommendation: weak
Evidence level: moderate
Consensus level: 97.4%

Comment

As indicated in statements 8A and 8B and in agreement with the Rome III criteria,[9 62] *H. pylori* infected dyspeptic patients with negative endoscopy who experience sustained symptom control are labelled as having *H. pylori*-associated dyspepsia. Conversely, when symptoms do not benefit in the long term from successful eradication, this indicates that *H. pylori* gastritis did not cause the symptoms in these patients. Consequently, they can keep the label 'functional dyspepsia' (figure 1).

Section 3 Diagnosis of gastritis

CQ12. Is it possible to make a diagnosis of atrophy and/or intestinal metaplasia by endoscopy?

Statement 12

Atrophic mucosa and intestinal metaplasia can be accurately detected by image-enhanced endoscopy, after appropriate training.

Grade of recommendation: strong
Evidence level: high
Consensus level: 84.2%

Comment

Conventional endoscopy is, in most hands, an inadequate tool for diagnosing atrophy and intestinal metaplasia and therefore it remains mandatory that a biopsy is carried out, allowing histomorphological assessment of the gastric mucosa according to the Sydney classification.[19 20] However, image-enhanced endoscopy has improved the accuracy and reproducibility of endoscopic diagnosis of premalignant gastric lesions. This includes chromoendoscopy,[65] high-resolution magnification endoscopy[66 67] and image-enhanced endoscopy combined with magnification[15 68–72] (figure 2). These methods are now routinely available in Japan and will be increasingly used worldwide. Adequate evaluation of the stomach mucosa with each of these methods requires appropriate training[66] and offers the advantage of targeted biopsies.

CQ13. Is the updated Sydney System appropriate for histological diagnosis of gastritis?

Statement 13

Accurate histological assessment of gastritis requires biopsy sampling of both antrum and corpus.

Grade of recommendation: strong
Evidence level: high
Consensus level: 92.1%

Comment

Premalignant lesions of the stomach may be unevenly distributed. Therefore, accurate histological assessment of gastritis requires biopsy sampling of both antrum and corpus. This may facilitate the classification and grading of preneoplastic gastric lesions.[73] Various studies have shown that more extensive biopsy sampling increases the diagnostic yield for identifying patients with premalignant lesions and provides a better overview of the severity and distribution of these lesions.[74–76] This also has practical limitations, which led to the updated Sydney System. This provides guidance on the methods of sampling and the histopathological grading of individual abnormalities—in particular, inflammation, gland loss and metaplasia.[20] The Sydney System recommends routine

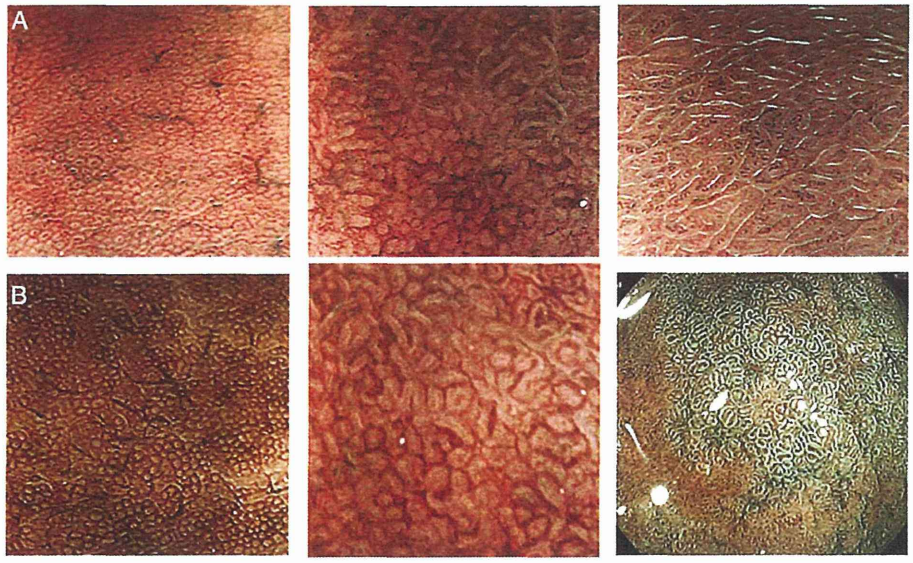

Figure 2 Image enhanced endoscopy. (A) Narrow band imaging (NBI) of the gastric mucosa. Round homogeneous sized pits with regularly arranged collecting venules are shown (left). This pattern (regular arrangement of collecting venules) named 'RAC' pattern in the corpus mucosa highly indicates a *Helicobacter pylori* negative state.[13] In the *H. pylori*-infected mucosa with inflammation, pit patterns are elongated, varied in sizes and shapes with spaces between them. Collecting venules are obscured owing to inflammation (centre).[14] When intestinal metaplasia develops, the pit pattern is further elongated with light blue lines (light blue crest sign) decorating the pits margins (right).[66] The images were provided by Dr Kazuyoshi Yagi. (B) Blue laser imaging (BLI) of the gastric mucosa. BLI is a new modality of image enhancement.[70] The BLI-bright mode can easily obtain lower magnification images, similar to the NBI images in (A) (left). With BLI-magnification mode, further mucosal details including periglandular capillary networks (red coloured circles surrounding the pits) are seen (centre). BLI endoscopy is useful for identifying the area of intestinal metaplasia where greenish coloured elongated pit patterns predominate (right). The images were provided by Dr Hiroyuki Osawa, Jichi Medical University.

sampling of five gastric biopsy specimens: antrum greater and lesser curvature, incisura and corpus greater and lesser curvature. Specimens need to be put into separate vials and grouped for each site or lesion. The system is widely used; the most common modification being to leave out the separate incisura sample.[36] It is of key importance that separate specimens are obtained from endoscopically visible lesions. The accuracy of image-enhanced endoscopy in trained hands further increases the yield of targeted biopsies.[66 77 78]

CQ14. Are grading systems such as OLGA and OLGIM useful for risk stratification?

Statement 14A

Gastric cancer risk correlates with the severity and extent of atrophic gastritis.

Grade of recommendation: strong
Evidence level: high
Consensus level: 94.7%

Statement 14B

Histological staging systems such as OLGA and OLGIM are useful for risk stratification.

Grade of recommendation: strong
Evidence level: low
Consensus level: 97.3%

Comment

Most gastric cancers are triggered by longstanding gastritis, primarily due to *H. pylori* infection. This can occur via a multistep pathway of precancerous lesions—in particular, atrophic gastritis, intestinal metaplasia and dysplasia/intraepithelial neoplasia. Various studies confirm an increased gastric cancer risk in patients with premalignant gastric lesions. For instance, a nationwide study from the Netherlands including approximately 98 000 patients with premalignant gastric lesions reported, on average, a 2–3% gastric cancer risk over 10 years.[79] This risk varied with the baseline stage of premalignant lesions, being 0.8%, 1.8%, 3.9% and 32.7% for patients with atrophic gastritis, intestinal metaplasia, mild-to-moderate dysplasia and severe dysplasia, respectively.[79]

These data confirmed the association between presence of premalignant gastric lesions and development of gastric cancer, yet also showed that the risk for developing gastric cancer in an individual with premalignant lesions is nevertheless small (2–6 per 1000 people per year). This necessitates the use of risk stratification methods.

Gastric biopsy sampling can be used to provide the most important information for risk classification. This led to the OLGA staging system.[16 17] This histological staging system grades patients with gastritis into stages with corresponding gastric cancer risk. Further studies showed that this staging system provides relevant clinical information.[80–82] Based on the high prevalence of atrophic gastritis in at-risk populations and the limited reproducibility and high interobserver variability in histological diagnosis of atrophic gastritis, a further proposal was made for the OLGIM system based on diagnosis and distribution of intestinal metaplasia.[18]

The interobserver reproducibility was improved for intestinal metaplasia compared with atrophic gastritis, and the correlation between the severities of gastritis remained at least as strong.[18] Subsequent studies with both the OLGA and OLGIM systems showed a higher gastric cancer risk in patients in stage III or IV of OLGA or OLGIM.[82–84] As a result, upper gastrointestinal surveillance endoscopy should be offered to patients in these subcategories.

CQ15. Are serological tests (pepsinogen I, II, I/II, *H. pylori* antibody) useful for risk stratification?

Statement 15

Serological tests (pepsinogen I and II and *H. pylori* antibody) are useful for identifying individuals at increased risk for gastric cancer.

Grade of recommendation: strong
Evidence level: high
Consensus level: 91.9%

Comment

Serological tests for the diagnosis of chronic gastritis and gastric atrophy have been in use for more than 25 years. These include *H. pylori* serology (crude antigen with or without additional determination of anti-CagA antibodies) for the diagnosis of gastritis, and serum pepsinogen I and II and gastrin for the diagnosis of gland loss resulting in hypoacidity.[85] These tests are usually applied in panels of multiple tests and have been shown to be a useful non-invasive diagnostic tool in an individual patient, and as a population screening and surveillance tool.[86 87] A Japanese cohort of 9293 screenees underwent serological assessment by means of *H. pylori* serology and pepsinogen I and II measurement.[86] The annual progression to gastric cancer was very low in subjects with normal pepsinogens, irrespective of *H. pylori* status. The annual progression to gastric cancer was substantially higher (3.5–6 per 1000 per year) in individuals with low serum pepsinogen levels, compatible with presence of atrophic gastritis.[86] In the latter group, the incidence of gastric cancer was higher among those with negative *H. pylori* serology than among those with positive *H. pylori* serology, which is indicative of progressive and widespread atrophy and metaplasia impairing further *H. pylori* colonisation. Similar findings were obtained in other studies.[88 89]

CQ16. When is it appropriate to search and screen for *H. pylori* gastritis?

Statement 16

Depending on the epidemiological context, it is appropriate to search and screen for *H. pylori* gastritis at an age before development of atrophic gastritis and intestinal metaplasia.

Grade of recommendation: strong
Evidence level: moderate
Consensus level: 97.3%

Comment

H. pylori infection is mainly acquired in childhood, up to the age of 12 years, in developed countries mostly by intrafamilial transmission.[90–92] The bacterium and associated gastritis persist lifelong, unless treated by eradication therapy, or unless end-stage widespread atrophic gastritis and intestinal metaplasia occur. The risk for gastric cancer depends on the grade of gastric atrophy and intestinal metaplasia.[31 82–84 86] *H. pylori* eradication can reduce the risk for cancer, but this effect is largely confined to patients without atrophy and metaplasia.[93–95] In patients with these lesions, *H. pylori* eradication reduces gastritis, but may not stop further progression to cancer. As a result, cancer can occur more than 10 years after *H. pylori* eradication treatment.[96] Against this background, it is appropriate to search and screen for *H. pylori* gastritis at an age when new infections become less likely (>12 years) and before development of atrophic gastritis and intestinal metaplasia. This all depends on the geographical location and epidemiological context, taking into account the prevalence of infection and age-related cancer incidence.[97]