Functional Dyspepsia

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Abstract

Functional dyspepsia (FD) is defined as a clinical condition in which pain arises from the gastroduodenal area in the absence of any organic, systemic, or metabolic disease that could explain the symptoms. Dyspeptic symptoms must be present for the previous 3 months with symptom onset at least 6 months before diagnosis according to the Rome III criteria. *Helicobacter pylori* (*H. pylori*) infection is considered a predisposing factor for FD, because *H. pylori* is known not only to induce pathologic change of the gastric mucosa but also to affect several gastrointestinal hormones. Furthermore, recent studies showed that *H. pylori* could influence molecular biology causing motility disorders. Unfortunately, the results are still controversial, and further studies are needed to evaluate the role of *H. pylori*. *H. pylori* eradication is suggested as one of the treatment options for FD. In countries with a high prevalence of *H. pylori* infection, such as Korea, *H. pylori* eradication might improve the symptoms of FD patients. Several meta-analyses reported that *H. pylori* eradication could improve symptoms in patients with FD compared to placebo; however, there are limitations, including heterogeneity of enrolled studies. Therefore, well-designed, prospective studies are required to confirm the effect of *H. pylori* eradication in FD.

Keywords

Disease eradication • Dyspepsia • *Helicobacter pylori*

18.1 Introduction

Dyspepsia is one of the most prevalent gastrointestinal diseases, and its prevalence is presumed to be about 5 % of all patients who visit primary healthcare clinics. Patients with dyspeptic symptoms usually suffer from heartburn, epigastric

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pain, postprandial discomfort, bloating, and a heavy feeling in the upper abdominal area. These symptoms are generally chronic and can decrease quality of life. Some patients with dyspeptic symptoms are diagnosed with functional dyspepsia (FD), which is defined as chronic and recurrent gastroduodenal discomfort without evidence of organic or systemic disease, such as peptic ulcer, gastrointestinal malignancy, gastroesophageal reflux disease, or pancreatobiliary disease. Of patients who were referred to the department of gastroenterology at a tertiary hospital in Korea, about 8–20 % had organic diseases, and about 70–92 % had functional gastrointestinal disorders (FGIDs). FD was the most common disorder among the patients with FGIDs [1]. According to the National Health Insurance Corporation database in Korea, FGIDs lead to a significant socioeconomic burden [2].

Several factors have been suggested to induce the symptoms of FD, including disturbed gastroduodenal motility, visceral hypersensitivity, psychological factors, and diet. Among them, the direct connection between *Helicobacter pylori* (*H. pylori*) infection and FD remains controversial. Given this background, the aims of this chapter are to evaluate the relationship between FD and *H. pylori* infection, to assess the role of *H. pylori* in FD pathogenesis, and to assess the effect of *H. pylori* eradication on treatment of FD.

18.2 Definition of Functional Dyspepsia

Prior to investigating the relationship between *H. pylori* infection and FD, we reviewed the definition of FD in detail. According to the Rome III criteria, FD is defined as the existence of symptoms seeming to originate in the gastroduodenal area but with a negative diagnostic workup for organic or metabolic diseases that would explain the pain, including upper endoscopy, abdomen ultrasonography, laboratory findings, computed tomography, or other modalities [3]. FD was divided into four symptoms based on the Rome III criteria as follows: epigastric pain, epigastric burning, bothersome postprandial fullness, and

early satiation (prevents finishing regular-sized meals). These symptoms must have been present for the previous 3 months with symptom onset at least 6 months before diagnosis. In addition, they presented two novel subcategories of FD based on cohort and population-based studies: postprandial distress syndrome (PDS) and epigastric pain syndrome (EPS) [4–6]. PDS must include one or both of the following symptoms: bothersome postprandial fullness after regular-sized meals at least several times per week and early satiety preventing finishing a regular-sized meal at least several times per week. In addition, patients with PDS can experience bloating in the upper abdominal area, postprandial nausea, or belching. Furthermore, PDS may coexist with EPS. EPS includes epigastric pain or burning of at least moderate severity at least once per week. This epigastric pain or burning should be intermittent, should not be generalized or localized to other abdominal or chest areas, should not be alleviated by defecation or passage of flatus, and should not be associated with gallbladder or sphincter of Oddi disorders. Additionally, the pain is usually induced or resolved by intake of a meal but may also happen during a fasting state [3, 7] (Table 18.1).

18.3 Pathophysiology of Functional Dyspepsia

FD is a complex disease that can arise from a variety of causes. Unfortunately, as stated above, the association between FD and *H. pylori* infection has not been clearly established. From the perspective of the Rome committee, *H. pylori* infection is not included as an organic cause of FD. Thus, *H. pylori*-infected patients with dyspeptic symptoms can be considered to have FD. Recently, several studies have suggested that the relationship between FD and *H. pylori* infection may play a role in FD pathophysiology.

Several studies have reported that some patients acquired irritable bowel syndrome (IBS) symptoms after a gastrointestinal infection. Similarly, several studies showed that a subset of patients developed FD following an episode of

Table 18.1 Rome III criteria for functional dyspepsia

Diagnostic criteria[a] for functional dyspepsia must include one or more of the following symptoms:
(a) Bothersome postprandial fullness
(b) Early satiety
(c) Epigastric pain
(d) Epigastric burning
With no evidence of structural disease that is likely to explain symptoms (including upper endoscopy)
1. Postprandial distress syndrome
Diagnostic criteria[a] must include one or both of the following symptoms:
(a) Bothersome postprandial fullness, occurring after ordinary-sized meals, at least several times per week
(b) Early satiety that prevents finishing a regular meal, at least several times per week
Other supportive criteria:
(a) Upper abdominal bloating or postprandial nausea or excessive belching can be present
(b) Epigastric pain syndrome may coexist
2. Epigastric pain syndrome
Diagnostic criteria[a] must include all of the following symptoms:
(a) Pain or burning localized to the epigastrium of at least moderate severity at least once per week
(b) The pain is intermittent
(c) Not generalized or localized to other abdominal or chest regions
(d) Not relieved by defecation or passage of flatus
(e) Not fulfilling criteria for gallbladder and sphincter of Oddi disorders
Other supportive criteria:
(a) The pain may be of a burning quality, but without a retrosternal component
(b) The pain is commonly induced or relieved by ingestion of a meal but may occur while fasting
(c) Postprandial distress syndrome may coexist

Modified from Lacy et al. [7] and Tally and Vakil [8]
[a]Criteria must be fulfilled for the previous 3 months with symptom onset at least 6 months before diagnosis

gastrointestinal infection [9, 10]. A recent meta-analysis reported that the odds ratio (OR) for the occurrence of post-infectious FD was 2.54 (95 % confidence interval [CI], 1.76–3.65) more than 6 months after acute gastroenteritis compared with the control [11]. Another meta-analysis found an OR of 2.18 (95 % CI, 1.70–2.81) for FD risk following acute gastroenteritis [12]. Taken together, gastrointestinal infection is associated with an increased risk of FD, supporting an inflammatory and immunological mechanism in the pathogenesis of FD [13]. *H. pylori* infection is the main cause of gastroduodenal inflammation [14] and provokes activation of a complex cytokine and chemokine response in the gastric mucosa [15], which may induce dyspepsia [16].

H. pylori infection induces gastric acid hypersecretion in the gastric antral mucosa [17]. Antral-predominant gastritis occurs in about 10–15 % of patients with *H. pylori* infection, likely due to gastric acid hypersecretion [18]. Patients with antral-predominant gastritis due to *H. pylori* infection showed decreased somatostatin release in the antral gland area, which leads to increased gastrin release with subsequent rise in acid secretion. This mechanism may explain dyspepsia.

In addition to clinical symptoms, *H. pylori* infection induces macroscopic and microscopic changes in the gastric mucosa that, along with lifestyle factors, may increase the risk of atrophic gastritis and intestinal metaplasia, leading to gastric cancer [19–21]. However, the results of studies that investigated the relationship between severity of histological gastritis and dyspepsia symptoms were varied. Czinn et al. [22] revealed an association between the severity of inflammation and epigastric pain. Likewise, another study group also revealed an indirect association between the severity of inflammation on the gastric corpus and the severity of symptoms [23]. However, there was no significant difference between the severity of dyspepsia symptoms and the severity of histological gastritis in other studies [24, 25]. Consequently, it is difficult to draw firm conclusions about the relationship between the severity of gastritis and the severity of dyspeptic symptoms, and further studies are needed to investigate this association.

Among the gastrointestinal hormones studied so far, ghrelin and leptin are representative hormones controlling appetite. Ghrelin promotes appetite and food intake and stimulates gastric emptying and gastric acid secretion [26]. These functions are partially achieved via vagal nerve pathways [27]. Plasma ghrelin concentrations are

elevated in gastroduodenal mucosal injury for the purpose of gastroduodenal cytoprotection [28, 29]. However, plasma ghrelin levels decrease in the severe gastric mucosal atrophic state induced by *H. pylori* infection [30, 31]. Thus, *H. pylori* infection may be related to induction of gastric motor dysfunction and reduction of appetite by suppression of ghrelin secretion [16]. Ghrelin may therefore play a role in the occurrence of FD, especially that related to *H. pylori*. Studies have revealed that patients with FD experience changing plasma ghrelin levels, which are frequently related to FD symptom scores [32, 33]. A few studies reported that plasma ghrelin levels were significantly decreased in dysmotility-like FD patients with postprandial fullness and/or early satiety [34, 35]. A recent study revealed that the Leu72Met (408C > A) single nucleotide polymorphism of the ghrelin gene was significantly related to early-phase gastric emptying in patients with FD [36]. Akamizu et al. [37] revealed that repeated ghrelin administration increased food intake in patients with FD; however, another study showed that there was no significant difference between patients with dysmotility-like FD and healthy controls [32]. Increased plasma ghrelin levels in patients with FD were also reported [38]. Leptin also activates vagal nerve terminals, decreases appetite, and enhances gastric mucin secretion [39]. Similar to ghrelin, leptin may induce the occurrence of FD. A study in Iran reported that serum leptin levels were higher in patients with dysmotility-like dyspepsia [40]. Moreover, *H. pylori*-infected patients had increased serum leptin concentrations and leptin mRNA expression in the gastric mucosa [40, 41], suggesting that *H. pylori* infection could cause decreased appetite by stimulating serum leptin secretion. Unfortunately, there are only a few studies investigating the correlation of *H. pylori*-positive FD patients with ghrelin or leptin. Thus, the association between gastrointestinal hormones and *H. pylori*-associated dyspepsia remains speculative.

A recent study evaluated the role of microRNAs (miRNAs) in gastric motility disorders related to *H. pylori* infection [42]. Expression levels of muscle-specific miRNAs in the stomach of *H. pylori*-infected mice, such as miR-1, miR-133a, and miR-133b, were downregulated. On the other hand, the expression profiles of histone deacetylase 4 and serum response factor, which are target genes of miR-1 and miR-133 to reinforce muscular hyperproliferation, were accelerated. Furthermore, notable thickening of the muscular layer in the gastric corpus of *H. pylori*-infected mice was identified on histologic examination. Additionally, gastric emptying was significantly enhanced in *H. pylori*-infected mice. Taken together, chronic *H. pylori* infection influences the expression of muscle-specific miRNAs, histone deacetylase 4, and serum response factor, which might induce hyperplasia of the gastric muscular layer and acceleration of gastric emptying in *H. pylori*-infected mice. Though no study has tested this proposed mechanism in humans, these results suggest new molecular biology perspectives and provide a theoretical underpinning for *H. pylori*-associated dyspepsia to be an organic disease rather than a functional disorder.

Current literature suggests increased duodenal acid secretion in patients with dyspeptic symptoms [43] and a relationship between duodenal eosinophilia and FD. When eosinophil counts in patients with FD and asymptomatic controls were investigated, the OR for FD patients with high eosinophil counts in the duodenal bulb and duodenal second portion were 11.7 (95 % CI, 3.9–34.9) and 7.3 (95 % CI, 2.9–18.1), respectively, compared with asymptomatic controls [44]. *H. pylori* infection induces eosinophil aggregation in the gastric mucosa [45]. Another recent study also reported that eosinophilia in the duodenal second portion was significantly increased in FD patients with postprandial fullness, early satiety, and abdominal pain [46]. Therefore, *H. pylori* infection might be related to duodenal eosinophilia alongside the occurrence of FD. Intraepithelial lymphocytes in patients with FD and healthy controls were also evaluated by a study in France [47]. The number of intraepithelial lymphocytes was significantly higher in *H. pylori*-positive FD patients compared to healthy controls, but there was no significant difference between *H. pylori*-negative FD patients and healthy controls. The expression of

CD95/Fas and HLA-DR expressing CD3+ intraepithelial lymphocytes was significantly lower in *H. pylori*-negative FD patients than in healthy controls. These results suggest that the phenotypic characteristics of intraepithelial lymphocytes might explain the difference between *H. pylori*-positive FD and *H. pylori*-negative FD.

Taken together, *H. pylori*-positive dyspepsia may represent a new area of study for FD. Recent studies suggested that *H. pylori*-positive dyspepsia, or *H. pylori*-associated dyspepsia, is not a functional disorder but an organic disease with many and various mechanisms of pathophysiology. Therefore, some study groups proposed that *H. pylori*-associated dyspepsia is different from FD and should be separated [16, 19]. A recent report from Kyoto global consensus clarified that *H. pylori* infection is the cause of dyspepsia in a subset of patients, and *H. pylori*-associated dyspepsia is a different entity compared to FD [48]. Further studies are needed to evaluate the true association between *H. pylori* infection and symptoms of FD.

18.4   Diagnostic Approach to Functional Dyspepsia

The committee of the American College of Gastroenterology issued guidance on the evaluation of FD patients [8]. Dyspeptic patients more than 55 years old or those with alarm features (Table 18.2) should undergo prompt endoscopy to rule out peptic ulcer disease, esophagogastric malignancy, and other rare upper gastrointestinal tract diseases. In patients aged 55 years or younger with no alarm features, the clinician may consider two approximately equivalent management options: (i) test and treat for *H. pylori* using a validated noninvasive test and a trial of acid suppression if eradication in successful but dyspeptic symptoms do not resolve, or (ii) an empiric trial of acid suppression with a proton pump inhibitor (PPI) for 4–8 weeks. The test-and-treat option is preferable in populations with a moderate-to-high prevalence of *H. pylori* infection (≥10 %), whereas the empirical PPI strategy is preferable in low prevalence situations (Fig. 18.1).

Table 18.2 Alarm features

(a) Bleeding
(b) Anemia
(c) Early satiety
(e) Progressive dysphagia
(d) Unexplained weight loss (>10 % body weight)
(f) Odynophagia
(g) Persistent recurrent vomiting
(h) A family history of gastrointestinal cancer
(i) Previous esophagogastric malignancy
(j) Previous documented peptic ulcer
(k) Lymphadenopathy
(l) Abdominal mass
(m) Fever
(n) Jaundice
(o) New onset dyspepsia[a]

Modified from Talley and Vakil [8] and Miwa et al.[49]
[a]Miwa et al. [49] defined age of new onset dyspepsia as over 40 years of age in populations with a high prevalence of upper gastrointestinal malignancy and over 45 and 50 years in populations with intermediate and low prevalence, respectively

In 2012, an Asian consensus report on FD was developed [49]. All of the consensus members agreed that if patients have any alarm features including new onset dyspepsia in a patient over 40 years of age in a population with high prevalence of upper gastrointestinal malignancy, such as China, Korea, or Japan, they should undergo further testing (Fig. 18.2). Compared to the guidelines of the West, those in Asia recommend a younger patient age at which new onset of dyspepsia should prompt endoscopic examination.

According to Korean guidelines for the treatment of FD in 2012, which compared endoscopy with "test and treat" for *H. pylori*, endoscopy may be a more effective initial strategy for managing patients with FD in Korea given the high incidence of gastric cancer and low cost of endoscopy [50]. The usefulness of *H. pylori* serology testing before endoscopy in patients with dyspepsia was investigated in Korea [51]. The sensitivity and negative predictive value of anti-*H. pylori* IgG for organic disease were 76.6 % and 85.5 %, respectively, in patients with dyspepsia under 40 years old. In patients with dyspepsia over 40 years old, the sensitivity and negative predictive value of anti-*H. pylori* IgG for organic dis-
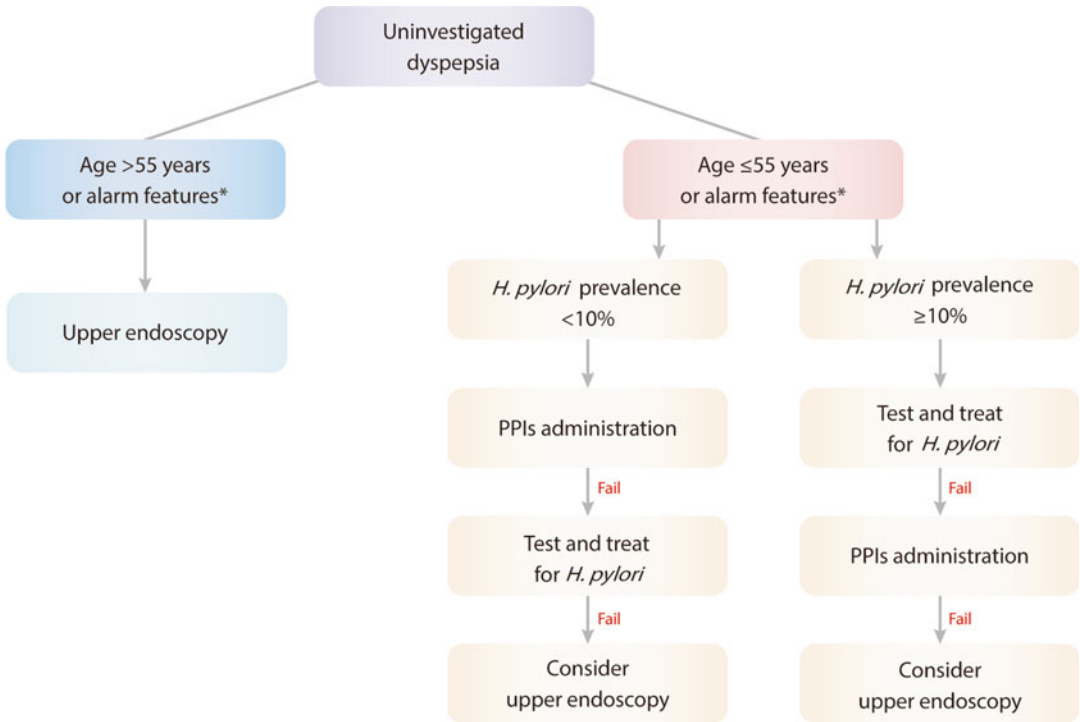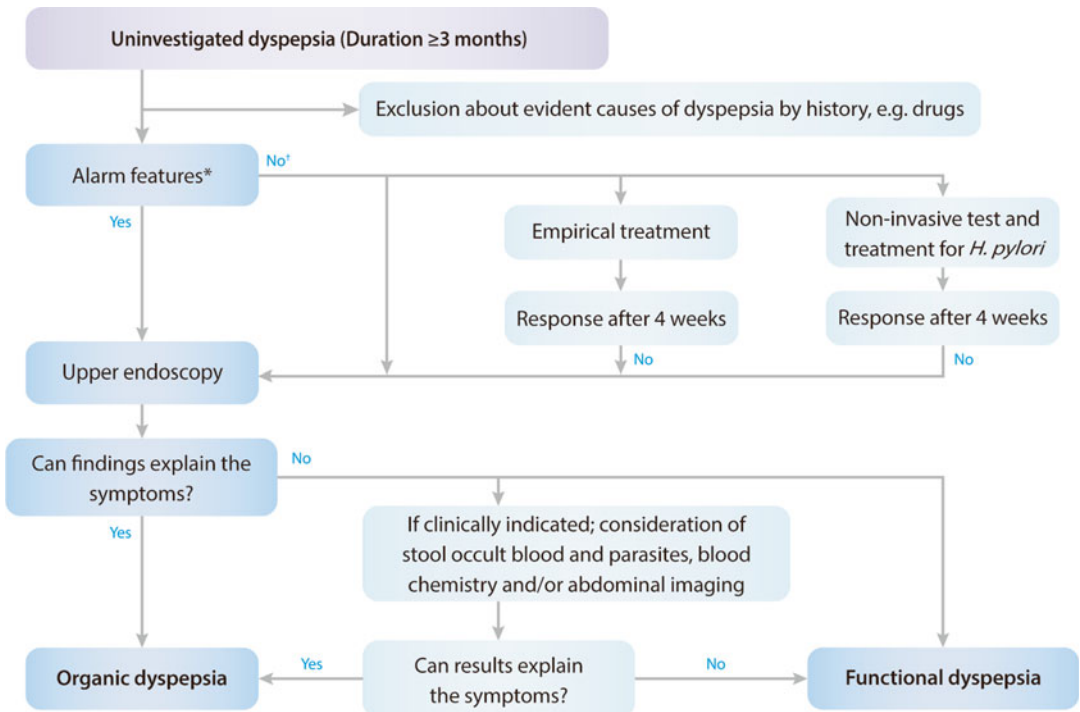
Fig. 18.1 Management algorithm of uninvestigated dyspepsia. *Alarm features can be found in Table 18.2. *H. pylori Helicobacter pylori*, *PPIs* proton pump inhibitors (Adapted from Tally and Vakil [8], with permission from nature publishing group)

ease were 61.9 % and 64.0 %, respectively. Although further study will be needed, the "test-and-treat" *H. pylori* approach might not the preferred initial step in treating patients with FD in Korea. Rather, as mentioned earlier, endoscopy may be the more effective initial strategy for managing patients with FD in Korea [50, 52].

Other diagnostic tests, such as serum testing for anemia, liver disease, and pancreatitis (amylase and lipase) and upper abdominal ultrasound or computed tomography, can be helpful in diagnosing FD [49].

18.5 Treatment of Functional Dyspepsia

There are several options for treating FD, including PPIs, histamine-2 receptor antagonists, prokinetic agents, and antidepressant and anxiolytic agents. Among them, we focus on *H. pylori* eradication.

Several epidemiologic studies have revealed that the *H. pylori* infection rate in patients with FD is higher than in matched control populations. A meta-analysis expressed a summary OR of 1.6 (95 % CI, 1.4–1.8) for *H. pylori* infection in FD [53]. Although this has not yet been confirmed, this result suggests that eradication of *H. pylori* could improve FD symptoms [54].

A Cochrane meta-analysis was performed on 17 randomized controlled trials and identified an association between *H. pylori* eradication and improvement in FD symptoms. A small but significant benefit of *H. pylori* eradication therapy was observed with a number needed to treat of 14 (95 % CI, 10–25) [55]. In another recent study, the number needed to treat was eight [43]. The cumulative long-term benefit of *H. pylori* eradication in patients with FD was also performed in UK. Dyspeptic symptoms in the *H. pylori* eradication group were significantly decreased compared to the placebo group, and OR was 0.84 (95 % CI, 0.71–1.00) [56]. The effect of *H. pylori* eradication on Asian FD patients might be different from FD patients in the West due to the varying prevalence of *H. pylori* strains including polymorphisms of *cagA* gene, gastric acid levels, and the severity of gastritis [57]. A systemic review and meta-analysis from China reported that the summary OR for improvement in FD patients after *H. pylori* eradication was 3.61 (95 % CI, 2.62–4.98) [58]. A study in Singapore demonstrated a 13-fold increased chance of FD symptom resolution in successfully eradicated *H. pylori* FD patients compared to those with persistent *H. pylori* infection (95 % CI, 1.1–17.7) [59]. In addition, a recent meta-analysis of randomized controlled trials with 12 months follow-up revealed that dyspeptic symptoms were significantly improved in eradication group (OR 1.38; 95 % CI, 1.18–1.62) [60]. Unfortunately, there are no randomized controlled studies evaluating the effect of *H. pylori* eradication on FD in Korea. Our study group showed that *H. pylori* eradication (OR 5.81; 95 % CI, 1.07–31.59) was related to improvement of FD at one year [61]. Studies in meta-analysis evaluated the effect of *H. pylori* eradication in patients with functional dyspepsia since 2000 and were summarized in Table 18.3.

However, Zullo et al. [63] pointed out several problems related to meta-analyses studying the effect of *H. pylori* eradication in FD patients. The type and number of dyspeptic symptoms of patients in enrolled studies were different, and the definitions of symptom improvement or regression varied widely. Many studies were performed to verify the effectiveness of *H. pylori* eradication in FD patients; however, only 12 studies were well-designed, double-blind, placebo-controlled studies with at least 50 patients followed for more than 6–12 months with final confirmation of *H. pylori* status by endoscopy with biopsy or a ^{13}C-urea breath test. Unfortunately, the type and

Fig. 18.2 Diagnostic algorithm of functional dyspepsia. *Alarm features can be found in Table 18.2. †The appropriate choice from the three options according to patient symptoms, patient wishes, risk of *H. pylori* infection, and gastric cancer in each country as well as primary healthcare settings. *H. pylori* *Helicobacter pylori* (Adapted from Miwa et al. [49], with permission from The Korean Society of Neurogastroenterology and Motility)

Table 18.3 Meta-analysis studies about *Helicobacter pylori* eradication in patients with functional dyspepsia since 2000

Authors	Year	Enrolled studies	Follow-up	Number	Symptom improvement	OR (95 % CI)	NNT
Gisbert et al. [62]	2002	9 RCT	At least 6 months	Patients; 953 Control; 958	Eradication group; 43 % (95 % CI, 40–46 %) Control group; 39 % (95 % CI, 36–42 %)	1.20 (0.91–1.58)	25
Moayyedi et al. [55]	2006	17 RCT	At least 3 months	Patients; 1,934 Control; 1,632	Eradication group; 36 % (range 15–75 %) Control group; 29 % (range 7–51 %)	0.90 (0.86–0.94), 10 % relative risk reduction (95 % CI, 6–15 %) in eradication group	14
Jin et al. [58]	2007	7 RCT	At least 1 month	Patients; 395 Control; 366	Eradication group; 74.4 % (294/395) Control group; 47.3 % (173/366)	3.61 (2.62–4.98)	NM
Zhao et al. [60]	2014	14 RCT	At least 12 months	Patients; 1,490 Control; 1,503	Eradication group; 40.6 % (605/1,490) Control group; 34.0 % (511/1,503)	1.38 (1.18–1.62)	15

OR odds ratio, *CI* confidence interval, *NNT* number needed to treat, *RCT* randomized controlled trials, *NM* not mentioned

number of symptoms and the definition of symptom improvement were different even in these 12 well-designed studies. Considering these findings, we could assume that the studies evaluating the effectiveness of *H. pylori* eradication in patients with FD are difficult to interpret. There is thus no definitive conclusion about the usefulness of *H. pylori* eradication in FD patients.

Despite these limitations, the American Gastroenterological Association recommends *H. pylori* eradication as the initial management strategy for uncomplicated dyspepsia in patients younger than 55 years, especially in countries with high prevalence (>10 %) of *H. pylori* infection, like Korea [7]. The Korean College of *Helicobacter* and Upper Gastrointestinal Research also reported that *H. pylori* eradication helps long-term dyspeptic symptom improvement in some patients with FD [64].

On another note, *H. pylori* eradication is useful in only some patients with FD. A recent study reported that FD patients with microscopic duodenitis showed greater symptom improvement after *H. pylori* eradication than those without microscopic duodenitis [65]. Sugano et al. [19] who proposed that *H. pylori*-associated FD should be separated from FD also suggested that FD patients with *H. pylori* infection should be treated before meeting criteria for a diagnosis of FD. Because *H. pylori* infection clearly influences pathological and physiological changes, residual dyspepsia symptoms after complete eradication of *H. pylori* infection might be regarded as real FD coexisting with *H. pylori* infection. Based on these considerations, the Kyoto global consensus also agreed that patients who remain symptomatic after successful *H. pylori* eradication should be regarded as having FD [48] (Fig. 18.3). In addition, *H. pylori* eradication is first-line treatment for dyspeptic patients with *H. pylori* infection, because eradication therapy for dyspeptic symptoms is better than placebo in *H. pylori*-infected dyspeptic patients.

All things considered, *H. pylori* eradication is effective in some patients with dyspepsia. Considering the short duration and acceptable
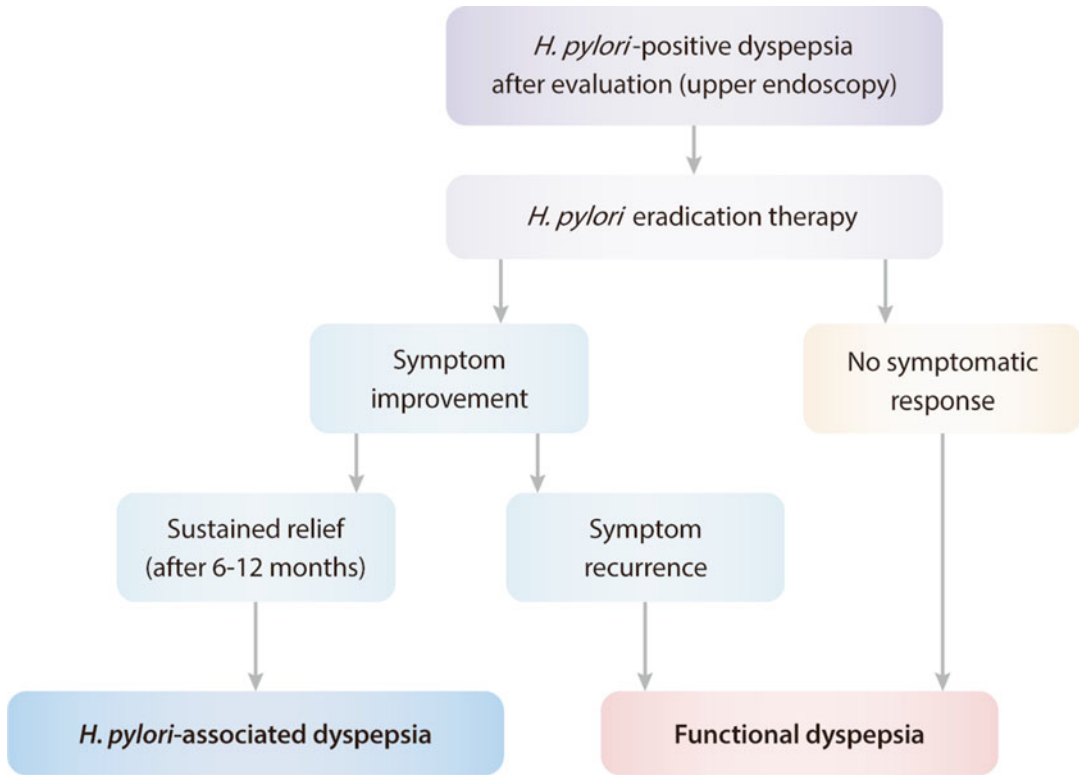
Fig. 18.3 Diagnostic algorithm of *H. pylori*-associated dyspepsia. *H. pylori Helicobacter pylori* (Adapted from Sugano et al. [48], with permission from BMJ publishing group Ltd.)

cost-benefit analysis for improving dyspeptic symptoms, *H. pylori* eradication could be proposed as the treatment for those with *H. pylori* infection.

Conclusions

FD is one of the most prevalent gastrointestinal disorders; however, many physicians are hard to diagnose FD due to the varied pathophysiology and symptoms. Among the many causes of FD, *H. pylori* infection is considered to have some effect on the onset of FD worldwide. *H. pylori* eradication is suggested as one of the therapeutic options for FD patients with *H. pylori* infection, and several meta-analyses reported that *H. pylori* eradication improved dyspeptic symptoms in FD patients compared to placebo. Thus, *H. pylori* eradication could be attempted for treatment of FD patients. Some limitations still exist, such as lack of well-designed, double-blinded, placebo-controlled studies to establish the effectiveness of *H. pylori* eradication in FD patients. Therefore, additional well-designed, prospective studies are needed to demonstrate the association between FD and *H. pylori* infection.

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