ORIGINAL ARTICLE

Proposed Algorithm for the Diagnosis and Management of Functional Dyspepsia in India

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Received: 23 July 2024; *Accepted:* 19 October 2024

Abstract

Disorders of gut–brain interaction (DGBI), formerly known as functional bowel disorders, encompass a diverse array of conditions and symptoms that may manifest in different parts of the gastrointestinal tract. Some of the most prevalent DGBIs include functional dyspepsia, irritable bowel syndrome, functional constipation, functional diarrhea, and functional bloating and distension. Around 80% of patients with dyspepsia have no identifiable organic cause and are labeled as functional dyspepsia. Globally, functional dyspepsia prevalence ranges from 11 to 30%. In India, physicians encounter 20–40% of patients with functional dyspepsia, with variations attributed to diagnostic criteria and regions. However, Indian clinical guidelines for functional dyspepsia are currently lacking. Fifty gastroenterologists participated in focus group discussions to create an India-specific algorithm for the diagnosis and management of functional dyspepsia. After several national and regional discussions among groups of gastroenterologists across India, an algorithm was finalized for careful and thorough clinical evaluation of patients presenting with chronic dyspeptic symptoms. This guidance document highlights the role of endoscopic evaluation and *Helicobacter pylori* infection in the diagnosis of functional dyspepsia, along with the role of proton pump inhibitors (PPIs) and prokinetics in its treatment. The experts also reviewed the use of several prokinetics and provided their views on the choice of drugs for varied clinical presentations of functional dyspepsia. Among prokinetics, the experts believed that itopride was the preferred and relatively safer option for the treatment of functional dyspepsia.

Journal of The Association of Physicians of India (2024): 10.59556/japi.72.0771

Introduction

Disorders of gut–brain interaction (DGBI), formerly known as functional bowel disorders, encompass a diverse array of conditions and symptoms that may manifest in different parts of the gastrointestinal tract. Some of the most prevalent DGBIs include functional dyspepsia, irritable bowel syndrome, functional constipation, functional diarrhea, and functional bloating and distension.[1] Dyspepsia is characterized by a collection of symptoms affecting the gastroduodenal region of the gastrointestinal tract, including epigastric pain, epigastric burning, postprandial fullness, or early satiety for 6 months or more. It is noteworthy that around 80% of individuals diagnosed with dyspepsia exhibit no identifiable structural cause for their symptoms, indicating the presence of functional dyspepsia.[2] Globally, the prevalence of functional dyspepsia has been reported to fall within the range of 11–30%. Similarly, a survey conducted in India indicated that approximately two-thirds of the participating physicians encountered 20–40% of patients with functional dyspepsia in a month, with 10–30% of these patients being newly diagnosed.[3] The observed differences in the reported prevalence of dyspepsia could be attributed to variations in the diagnostic criteria employed or to actual disparities in prevalence across different regions of the country.[4] Despite observing a significant prevalence of functional dyspepsia in Asian populations, most of the defining characteristics of functional dyspepsia have been derived primarily from data from Western regions.[5] In the clinical setting, symptoms experienced by patients with functional dyspepsia are influenced by multiple factors, including dietary constituents and body habitus. These factors are known to exhibit variations between Western and Asian populations. Additionally, cultural attitudes, healthcare-seeking behavior, and resource utilization differ between populations, and these factors are important indicators of the impact of functional dyspepsia.[6] These variations lead to notable differences in its global epidemiology and clinical characteristics. An Indian study on health-related quality of life (HRQOL) assessment in patients with functional dyspepsia showed poor HRQOL with severe dyspepsia and longer duration of symptoms.[7] Another study on various functional gastrointestinal disorders (FGIDs) among students at a north Indian college pursuing medical, nursing, and humanities courses observed that risk factors for occurrence of functional dyspepsia included female gender, enrollment in a medical course, consumption of junk food, a nonvegetarian diet, consumption of tea/coffee, and anxiety.[8] Emphasizing Indian clinical data becomes pivotal in understanding common pathogenetic factors specific to the country. Additionally, guidelines and recommendations catering to the Indian setup are currently missing. Recognizing the significance of addressing this extensively prevalent gastrointestinal disorder, a set of focus-group discussions among 50 gastroenterologists was conducted to reach consensus on an algorithmic approach for the diagnosis and management of functional dyspepsia, specifically tailored for primary care physicians in India.

Five group discussions were conducted to develop an algorithm for diagnosing and managing functional dyspepsia in India, starting at the primary healthcare level. A group of 10 gastroenterologists from across India first formulated an initial framework for the algorithm. Sections of the algorithm that exhibited ambiguity or lacked consensus were further discussed in subsequent regional meetings. Three regional meetings were conducted, each involving 12 experts from distinct regions of India: the South region, the North and West regions, and the East region. During these meetings, experts shared their opinions based on clinical experience and practices in their respective regions. Based on the inputs gathered during the regional meetings, the algorithm was modified to incorporate all views. Subsequently, some members from the first meeting and a few others further discussed and finalized the algorithm. A consensus was successfully

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How to cite this article: Zargar SA, Mohan VG, Shankar RB, *et al.* Proposed Algorithm for the Diagnosis and Management of Functional Dyspepsia in India. J Assoc Physicians India 2024;72(12):34–39.

achieved for all components within the algorithm, including history and physical examination, alarm symptoms, laboratory investigations, endoscopy, *Helicobacter pylori* (*H. pylori*) test, and the management strategy for the disease.

Diagnosis of Functional Dyspepsia

The diagnosis of functional dyspepsia relies on identifying characteristic dyspeptic symptoms, reviewing the patient's medical history, and excluding other upper gastrointestinal tract and upper abdominal conditions that may manifest similar dyspeptic symptoms.[5]

Patients experiencing chronic dyspepsia may present with bothersome symptoms categorized into two main subtypes: epigastric pain syndrome (EPS), characterized by epigastric pain and epigastric burning, and postprandial distress syndrome (PDS), characterized by early satiety, bloating, nausea, vomiting/retching, and decreased appetite. The Rome IV criteria require the absence of any evidence suggesting a structural disease leading to these symptoms and that they have persisted for the last 3 months, with an onset at least 6 months prior to diagnosing functional dyspepsia.[9]

History-taking and Clinical Examination

A variety of organic, systemic, or metabolic conditions are known to cause symptoms resembling those observed in functional dyspepsia, including peptic ulcer disease, gastrointestinal and hepatobiliary tract cancers, parasitic infestations, chronic pancreatic diseases, hyperthyroidism, hypothyroidism, chronic renal failure, electrolyte imbalances, and the potential influence of medications.[5] The experts believed that thoroughly evaluating and ruling out such potential causes of the above-mentioned gastrointestinal symptoms is of utmost importance (Fig. 1). It is also crucial to help identify the presence of any alarm symptoms (Fig. 2) by conducting detailed and careful history-taking.[5,10–13]

The presence of alarm symptoms warrants prompt investigations, wherein an upper gastrointestinal tract endoscopy would be required.[5,11] The experts believed that in patients aged over 45 years, various organic impairments, including malignancy, may cause chronic dyspeptic symptoms; and in areas with a high prevalence of gastric malignancy, an age over 37 years may indicate the need to screen for malignancy.[5,11] Similarly, the causes for recurrent vomiting, weight loss, dysphagia, evidence of gastrointestinal bleeding, hematemesis, or melena should be investigated promptly.[5] Immediate screening is recommended for patients with a family history of malignancy to rule out malignancy as a potential cause of chronic dyspeptic symptoms.[5] In addition to the abovementioned factors, new-onset dyspepsia can also be considered an alarm sign in patients above 40 years of age in areas with a high prevalence of upper gastrointestinal tract malignancy, and in patients over 45 and 50 years in areas with intermediate and low prevalence, respectively.[5]

The experts recommended checking for signs of anemia, abdominal lump, and lymphadenopathy during the physical examination of patients. Additionally, a positive Carnett's sign would indicate that the pain originates from the abdominal wall.

- Systemic illnesses like cardiac diseases*
- Metabolic diseases like diabetes and thyroid, and calcium-related metabolic diseases*
- Small intestinal bacterial overgrowth, giardiasis
- Medication and drug interactions related symptoms
- Fatty liver*, gallstones, chronic pancreatitis
- Parietal etiology of abdominal pain*
- If postprandial symptoms, rule out gastroparesis by looking for diabetes and neuropathic complications
- Lactose intolerance
- Connective tissue disorders

Fig. 1: Conditions to rule out before diagnosing functional dyspepsia[5,10–13]; *Opinion of the Indian expert gastroenterologists

- Age >45 years (in areas with a high prevalence of gastric cancer: >37 years)*
- Recurrent vomiting
- Weight loss
- Dysphagia
- Evidence of bleeding
- Family history of cancer
- Hematemesis*
- New onset dyspepsia in subjects
  - >40 years of age in a population with a high prevalence of upper gastrointestinal malignancy and
  - >45 and >50 years in populations with intermediate and low prevalence of upper gastrointestinal malignancy, respectively

Fig. 2: Alarm symptoms to investigate in patients with dyspepsia[5,11]; *Opinion of the Indian expert gastroenterologists

Investigations

The Asian consensus report states that most patients with dyspeptic symptoms can be diagnosed with functional dyspepsia based on their clinical symptoms and results of upper gastrointestinal tract endoscopy. Besides routine laboratory tests, some cases may require additional investigations, such as upper abdominal ultrasonography (particularly in regions with a high incidence of liver cancers) and stool examination for parasites and occult blood if needed.[5] The experts recommended conducting basic laboratory tests, such as complete blood count (CBC), serum electrolytes, fasting blood glucose (FBG), renal function tests, thyroid function tests, liver function tests, stool tests, and an ultrasonography examination to help detect or rule out the underlying cause of dyspeptic symptoms to reach a closer diagnosis of functional dyspepsia.[5]

Depending on the presence or absence of alarm symptoms, patients presenting with dyspeptic symptoms can undergo investigations to identify the probable source of their symptoms or be managed with empirical treatment based on their predominant symptoms.[11,14] Diagnosing functional dyspepsia according to the definition by the Rome IV criteria implies that potential underlying organic disorders have been excluded with an endoscopy.[11] The consensus reached on endoscopy is similar to various other guidelines that have universally recommended timely upper gastrointestinal tract endoscopy for patients aged over 45–60 years with dyspeptic symptoms to rule out neoplasia and determine *H. pylori* status through biopsies. Additionally, endoscopy is necessary for younger patients who present

with alarm features.[11] The experts believed that endoscopy should be the first choice of investigation in patients who elicit any of the alarm signs.[10] They also recommended endoscopy for patients without alarm symptoms who have not responded to previous treatment with proton pump inhibitors (PPIs).[15] Abnormal findings during endoscopy may indicate the organic cause of the dyspeptic symptoms, whereas a normal endoscopy can lead to the diagnosis of functional dyspepsia after ruling out *H. pylori* etiology.[5]

In an Asian consensus report, *H. pylori* eradication was strongly advised even in the absence of dyspeptic symptoms, particularly in certain Asian countries with a high prevalence of gastric cancer.[5] Similarly, a European consensus report also recommended testing for *H. pylori* in all patients with dyspeptic symptoms, either through noninvasive methods or gastroscopy. The report mentioned that patients with dyspepsia who test positive for *H. pylori* gastritis should be classified as having functional dyspepsia only if their symptoms persist for 6–12 months after *H. pylori* eradication. On the other hand, patients with dyspepsia and *H. pylori*-negative gastritis should be considered to have functional dyspepsia. A subset of patients with dyspepsia who exhibit a normal endoscopy and are *H. pylori* positive may show improvement in symptoms after eradication therapy, and this is referred to as *H. pylori*-associated dyspepsia.[11] The experts mentioned that rapid urease test (RUT) or gastric biopsies can determine the presence of *H. pylori* infection. However, the experts noted that with limited data to validate results of the RUT, it may be difficult to reliably reassess the presence of *H. pylori* or its eradication. Among the other *H. pylori* tests, the C13 urea breath test is expensive and not available in India, while the C14 breath test was banned due to radiation hazards. When results from C13 to C14 urea breath tests were compared, there were discrepancies, with no validation available.

The experts believed that *H. pylori* tests can be performed during endoscopy, and if the results are positive, *H. pylori* eradication therapy should be initiated.[11] The response to the eradication therapy should be assessed by retesting for *H. pylori* after 30 days of treatment.[16] If the dyspeptic symptoms persist despite a negative retest for *H. pylori*, a diagnosis of functional dyspepsia is more likely.[11] Patients who show improvement of symptoms along with a negative retest are referred to as having *H. pylori*-associated dyspepsia.[11] In some patients, the *H. pylori* retest may be positive posteradication therapy, indicating a resistant *H. pylori* infection. The experts advised prescribing a modified regimen of eradication therapy to such patients and a further re-test after 30 days to confirm the diagnosis of *H. pylori*-associated dyspepsia.[16,17] The experts were of the opinion that additional investigations, such as plain X-ray abdomen, gastric scintigraphy, electrogastrography (EGG), computed tomography scan, celiac serology (only in areas with a high prevalence of celiac disease), or endoscopic deep duodenal biopsies for histopathology to rule out eosinophilic enteritis, can also aid in supporting the diagnosis of functional dyspepsia or ruling out other causes of chronic dyspeptic symptoms.[5,18,19]

Management of Functional Dyspepsia

Managing symptoms of functional dyspepsia can pose difficulties due to the presence of overlapping disorders and the involvement of various mechanisms, including gastric acid hypersecretion, visceral hypersensitivity, or gastroduodenal dysmotility.[20]

Acid Suppressing and Neutralizing Therapies

Treatment with PPIs has shown significant benefits in patients with functional dyspepsia. Their effect, however, may be limited to patients with symptoms of EPS, while those with symptoms of PDS may not respond to PPIs.[11,21] The role of H2 receptor antagonists (H2RAs) in functional dyspepsia remains controversial, despite evidence sometimes suggesting that they can be efficacious in a subset of patients with functional dyspepsia. H2RAs are not recommended as first-line treatment for functional dyspepsia; however, they are widely used in clinical practice, particularly when PPIs are ineffective.[20] Alginates with antacids may be useful in reducing dyspeptic symptoms such as epigastric pain.[22] The experts believed that acid-neutralizing/suppressing therapy in functional dyspepsia may include the use of PPIs, H2 receptor antagonists (H2RAs), alginates, and antacids. Dietary advice and medications that improve digestive function are more likely to be beneficial in patients with symptoms of PDS that show abnormal gastric function.[22] Tailoring dietary advice to the specific functional dyspepsia subtype, including a low fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAP) diet for postprandial distress and bloating, could significantly improve symptoms and quality of life.[23]

Prokinetics

A review addressing prokinetic efficacy revealed that in PDS, dopamine receptor antagonists including metoclopramide, domperidone, levosulpiride, and itopride exhibited responder rates of approximately 59–81%, serotonin receptor agonists such as prucalopride from 32 to 91%, and muscarinic receptor antagonists such as acotiamide ranged from 31 to 80%.[24] The experts agreed that itopride improves gastrointestinal motility in functional dyspepsia and is reported to be efficacious and well-tolerated.[25] It was found comparable in efficacy to domperidone in relieving symptoms and was devoid of cardiac side effects.[26] For patients with nonulcer dyspepsia, a study reported higher complete symptomatic relief rates with itopride (81%) compared to domperidone (70%). Another study demonstrated significantly greater moderate to complete symptomatic relief with itopride (90%) in comparison to levosulpiride (83.3%) for patients with nonulcer dyspepsia ($p = 0.0146$).[24] Among various prokinetics used for functional dyspepsia, itopride may be the favorable choice for vulnerable groups, including the elderly and patients with diabetes.[24] It produces no undesirable cardiac effects due to its lack of affinity for the 5-HT4 receptors in the heart and no extrapyramidal side effects or hyperprolactinemia.[27] Acotiamide is useful for the relaxation of the fundus in PDS.[28] However, a clinical study reported that acotiamide has limited efficacy in patients with EPS and gastric acid hypersecretion.[29] Baclofen is known to act by inhibiting the postprandial increase in TLESRs.[30]

For patients with the EPS subtype of functional dyspepsia, the experts suggested first-line treatment typically with a PPI, while a prokinetic agent is considered as a second-line therapy.[10,11] Neuromodulators can be added if both the first-line and the second-line treatments are inadequate or fail to improve symptoms.[14] The PDS subtype of functional dyspepsia can be treated with prokinetics as first-line therapy, with the addition of a PPI and neuromodulators as second-line and third-line treatment, respectively.[10] The EPS-PDS overlapping subtype of functional dyspepsia can be treated using a combination of PPI and prokinetics, with the option of neuromodulators if required. Treatment response should be assessed in 4–6 weeks and modified if needed.

The experts concluded that prokinetics including itopride, cinitapride, acotiamide, baclofen, domperidone, levosulpiride, prucalopride, and metoclopramide may be used in patients with functional dyspepsia. For

delayed gastric emptying, experts preferred prokinetics such as itopride, levosulpiride, and domperidone and believed that levosulpiride may not be the prokinetic of choice for the elderly and should not be used in those with a family history of extrapyramidal disorders like Parkinson's disease. Caution should be exercised with the use of levosulpiride. Patients should be counseled and checked for extrapyramidal side effects in follow-up, especially in the older age groups. Immediate discontinuation of levosulpiride is advised if any warning signs are noted.[31] Domperidone and levosulpiride can potentially cause galactorrhea as a side effect, and patients must be informed about it.[32] Therefore, the experts considered itopride as a relatively safer option.

The experts considered acotiamide as the preferred choice only for impaired fundic accommodation. A water load test performed before an EGG can help identify fundic accommodation defect, indicated by a patient's inability to drink more than 300 mL of water at a time. Experts, however, believed that acotiamide is slower in action, as compared to other prokinetics, and relief is usually seen after 1 or 2 weeks. Overall, among all the prokinetic options, itopride was the preferred option as agreed upon by the experts.

Neuromodulators and Psychotherapy

Neuromodulators, including antidepressants for the relief of pain, may be useful in patients with EPS.[14] Amitriptyline, mirtazapine, selective serotonin reuptake inhibitors (SSRIs), and serotonin–norepinephrine reuptake inhibitors (SNRIs) may be beneficial, according to experts, as third-line therapy for functional dyspepsia. Psychotherapy in the form of hypnotherapy and lifestyle modifications, such as incorporating yoga and exercise into the daily routine, may benefit patients with functional dyspepsia. The various treatment options are listed in Figure 3.

Proposed Algorithm for the Diagnosis and Management of Functional Dyspepsia

Based on the focus-group discussions, the experts developed the algorithm shown in Figure 4 to help physicians in India in the diagnosis and management of functional dyspepsia. The algorithm features key steps that include a thorough initial evaluation of the patient, identification and ruling out of alarm symptoms, followed by endoscopy and *H. pylori* testing as the two key investigations that can help reach the diagnosis of functional dyspepsia. Considering the high prevalence of *H. pylori* infection in the Indian population, *H. pylori*-positive patients and their management with eradication therapy are also part of the algorithm. Patients can be managed with empirical pharmacological treatments based on their predominant dyspeptic symptom or by classifying the type of functional dyspepsia into either EPS, PDS, or EPS-PDS overlap. Treatment options include PPIs, prokinetics, and neuromodulators, among others listed in Figure 3.

Conclusion

Functional dyspepsia exhibits variations in Western and Eastern populations concerning sociodemography, lifestyle habits, dietary preferences, response to *H. pylori* eradication, and economic implications. Thus, despite being prevalent worldwide, its epidemiology and clinical characteristics differ significantly between these populations. Emphasizing data from the Indian clinical setting is important, as the Indian perspective will be useful for understanding the common pathogenetic factors here. To provide relevant guidance for primary care physicians in India, this consensus statement aims to articulate the experience and views of Indian experts. We anticipate that this statement will facilitate prompt and accurate management of functional dyspepsia, thereby alleviating its socioeconomic burden in the country.

Author Contributions

All the authors contributed to the acquisition and summarizing of literature, conduct of the focus-group discussions, development of consensus and the proposed algorithm, and review of all drafts of the manuscript, including the draft approved for submission.

Acknowledgments

The authors thank all the participating gastroenterologists for their generous time and invaluable clinical insights that helped this project reach its planned objective. Additionally, the authors thank Medicca Press Ltd. for medical writing and editorial assistance.

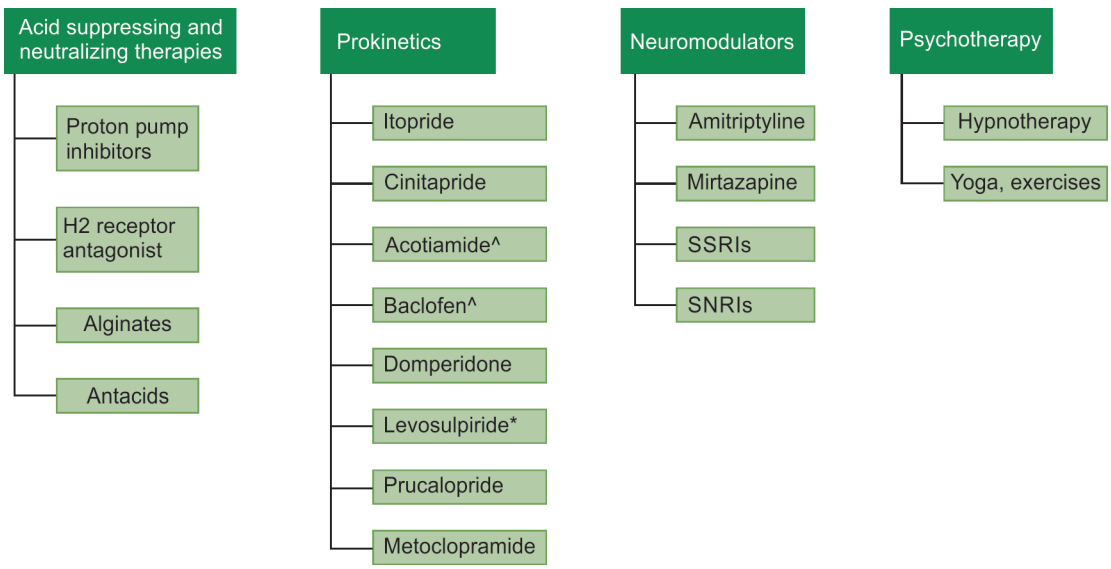

Fig. 3: Treatment options for patients with functional dyspepsia; ^Useful for fundus relaxation/PDS type of FD only. *Caution is advised with the use of levosulpiride. Counsel patients and follow up to check for extrapyramidal side effects, especially in older populations; SSRI, selective serotonin reuptake inhibitors; SNRI, serotonin and norepinephrine reuptake inhibitors

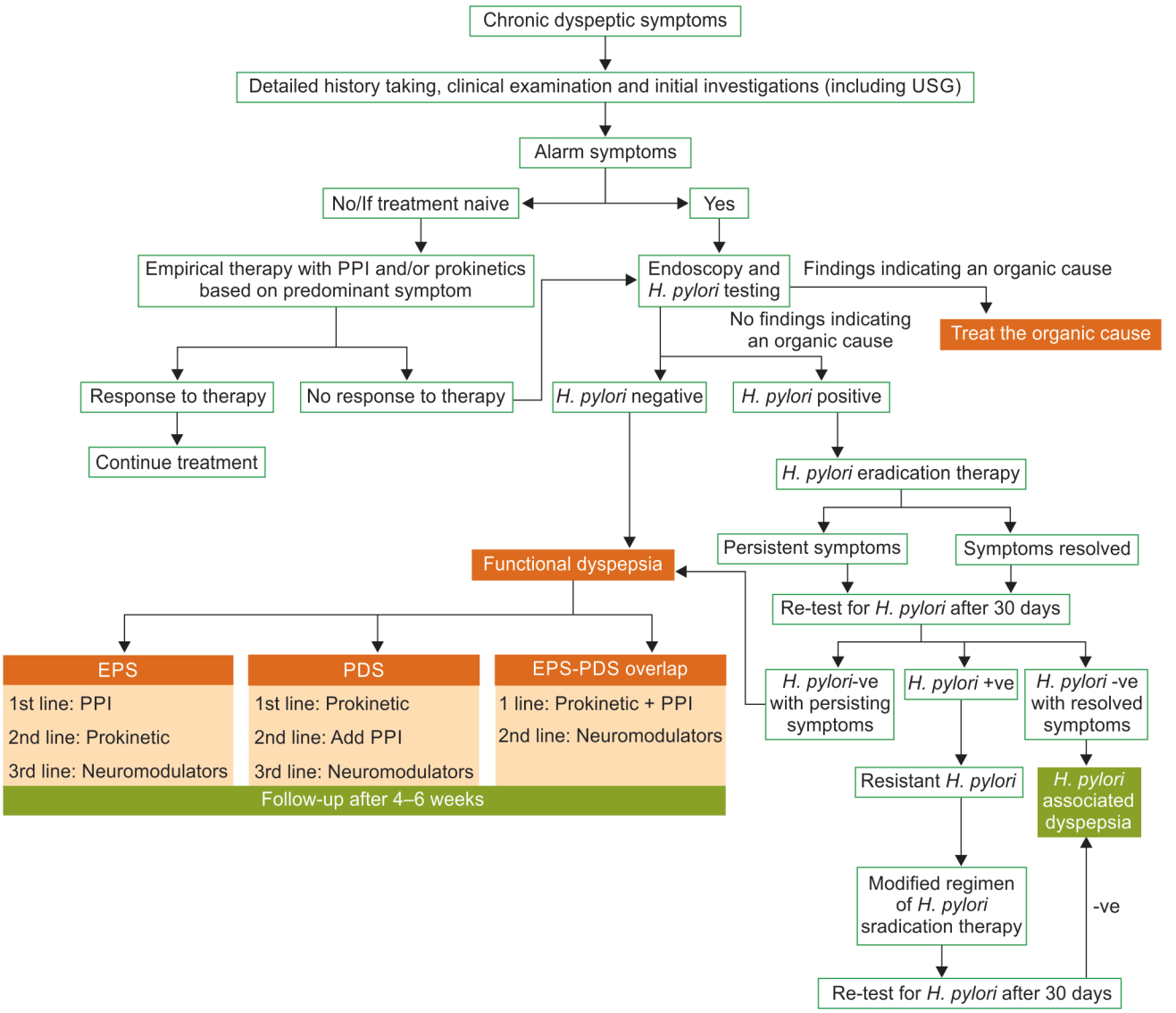

Fig. 4: Algorithm developed for the diagnosis and management of functional dyspepsia; EPS, epigastric pain syndrome; *H. pylori*, *Helicobacter pylori*; PDS, postprandial distress syndrome; PPI, proton pump inhibitors

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