Review Article

Proposed Algorithm for the Diagnosis and Management of Functional Dyspepsia-Gastroesophageal Reflux Disease Overlap in the Indian Clinical Setting

V G Mohan Prasad[1], B Ravi Shankar[2], Showkat Ali Zargar[3], Nitesh Pratap[4], Chetan Bhatt[5], Rajesh Puri[6], Jejoe Karankumar[7]

Abstract

Background : Functional Dyspepsia (FD) and Gastro-esophageal Reflux Disease (GERD) are common gastrointestinal disorders worldwide, impacting Quality of Life and healthcare costs. FD is characterized by epigastric pain and discomfort without organic causes, while GERD is marked by heartburn and acid reflux. In India, there is a high prevalence of FD-GERD overlap, often influenced by *Helicobacter pylori* infections and unique cultural factors. To address these challenges, an algorithm for managing FD-GERD overlap in India has been developed that will assist clinicians in accurate diagnosis and treatment, with the aim to reduce burden and improve patient outcomes. After several national and regional discussions amongst groups of Gastroenterologists across India, an algorithm was finalized for careful and thorough clinical evaluation of patients presenting with chronic dyspepsia and reflux symptoms. The algorithm highlights the role of endoscopic evaluation, *H. pylori* infection, and gastric pH monitoring in the diagnosis of FD-GERD overlap, along with the role of Proton Pump Inhibitors (PPIs) and prokinetics in its treatment. Among the various prokinetics, the experts agreed that itopride improves gastrointestinal motility in FD and is reported to be efficacious and well tolerated.

Key words : Functional Dyspepsia, Gastroesophageal Reflux Disease, Gastrointestinal Disorders, Algorithm, Prokinetics.

Functional Dyspepsia (FD) and Gastro-esophageal Reflux Disease (GERD) are common gastrointestinal disorders that significantly affect Quality of Life and increase healthcare costs[1]. According to Rome IV criteria, FD is defined by chronic or recurrent epigastric pain or discomfort without identifiable organic cause, often with early satiety, postprandial nausea, and bloating[1]. FD, a diverse condition is classified into Postprandial Distress Syndrome (PDS) and Epigastric Pain Syndrome (EPS), with or without overlapping features[2]. On the other hand, GERD is characterized by heartburn and regurgitation due to acid reflux, often accompanied by a bitter taste, chest pain and substernal burning and pain[1]. GERD includes Erosive Reflux Disease (ERD) and Non-erosive Reflux Disease (NERD) with nearly 70% of cases being NERD, where typical symptoms occur without visible mucosal damage on endoscopy[3].

Editor's Comment :

- FD-GERD overlap is common and challenging to manage. Accurate diagnosis is essential and prokinetics play a key role in treatment by addressing motility-related symptoms. Prokinetics like itopride can effectively relieve overlapping dyspeptic and reflux symptoms, improving patient outcomes in this complex condition.

Although FD and GERD are distinct gastrointestinal disorders, considerable symptom overlap is common, leading to diagnostic and therapeutic challenges[3-5]. Most existing data are based on studies from Western populations, with limited research from India. The prevalence of FD-GERD overlap in Indian studies is reported at 59%. In a study by Shankar, *et al* around 60% of Physicians observed 20-40% of their patients exhibiting overlapping symptoms, with 5-20% newly diagnosed[6]. In India, Helicobacter pylori (*H pylori*) is a key contributor to dyspeptic symptoms in FD but it may reduce severity of GERD disease[7,8]. Hence,

[1]MD, DM, Founder and Chairman, Department of Gastroenterology, VGM Gastro Centre, Coimbatore, Tamil Nadu 641005
[2]MD, DNB, DM, Director, Department of Medical Gastroenterology, Yashoda Hospitals, Secunderabad 500003, Telangana and Corresponding Author
[3]MBBS, DM, Director, Consultant, Department of Gastroenterology, Bismillah Medical Centre, Srinagar, Jammu and Kashmir 190008
[4]MBBS, DNB, Consultant Gastroenterologist, Department of Gastroenterology, KIMS Hospital, Secunderabad, Andhra Pradesh 500003
[5]MBBS, MD, DNB, Head, Department of Gastroenterology, Sir H N Reliance Hospital, Mumbai, Maharashtra 400007
[6]MBBS, MD, DNB, Senior Director, Department of Interventional Gastroenterology, Medanta Institute of Digestive and Hepatobiliary Sciences, Gurugram, Haryana 122001
[7]MBBS, MD, Medical Director, Department of Gastroenterology, Abbott India Ltd, Mumbai, Maharashtra 400051
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testing for *H. pylori* is important in FD-GERD overlap for optimal management. The clinical presentation in India is shaped by a complex interplay of *H. pylori* infection, cultural and physiological factors, dietary patterns, genetic and environmental influences.[5-8]

Effective management of FD-GERD overlap necessitates a comprehensive approach involving accurate diagnosis, evidence-based treatment, and individualized care[1,4]. However, guidelines and recommendations specifically tailored for the Indian set-up are currently missing. Thus, there is a need for algorithm development that can aid healthcare professionals in accurately identifying and managing FD-GERD overlap cases in India.

Hence, to develop a structured algorithm for the diagnosis and management of FD-GERD overlap, focus-group discussions were conducted with 50 Gastroenterologists from across India. Consensus was achieved on all key components, including patient history, physical examination, identification of alarm symptoms, relevant laboratory investigations, endoscopy, *H. pylori* testing, and the overall management strategy.

This review presents the resulting expert consensus algorithm tailored to the Indian context. It aims to facilitate timely and accurate diagnosis, reduce the Socio-economic burden, and improve patient outcomes by integrating clinical evidence, expert opinion, and population-specific considerations.

Diagnosis of FD-GERD Overlap :

The experts recommended looking for overlapping symptoms of GERD and Functional Dyspepsia (FD), such as epigastric pain, early satiety, bloating, nausea, and vomiting (FD), and heartburn, regurgitation, acidic or bitter taste, chest pain, and substernal burning (GERD)[1,3]. They also emphasized identifying atypical or extra-esophageal manifestations including non-cardiac chest pain, otitis media, asthma, chronic sinusitis, dental erosions, aphthous ulcers, halitosis, pharyngitis, laryngitis, laryngospasm, globus, postnasal drip, frequent throat clearing, tracheobronchitis, chronic cough, aspiration pneumonia, pulmonary fibrosis, chronic bronchitis, bronchiectasis and sleep apnea[9].

History-taking and clinical examination :

Evaluation of patients should begin with detailed history taking, clinical examination and initial investigations, including an Ultrasound Examination (USG) for ruling out potential causes other than FD and GERD. This should also help identify the presence of any alarm symptoms (Table 1), related to malignancies that help in further investigations and treatment.

Investigations :

The initial investigations include a Complete Blood Count, Serum Electrolytes, Fasting Blood Glucose, Renal Function Tests, Thyroid Function Tests, Liver Function Tests and USG to determine patient's overall health, with additional investigations like celiac serology in high prevalence areas[5]. Endoscopy remains essential to confirm FD by excluding organic disease[4].

For some patients with reflux esophagitis, a meal can produce gastric distension contributing to postprandial fullness. Duodenal eosinophilia, increasingly reported in FD, may explain the overlap, with research indicating that FD, especially PDS, is linked to increased GERD risk when duodenal eosinophilia is present, which can be identified via duodenal biopsy[4,10]. Additionally, duodenal hypersensitivity, plays a role in FD symptoms. This complex interplay between impaired gastric function, duodenal eosinophilia, and hypersensitivity contributes to the shared clinical manifestations in FD and GERD patients.[10] The assessment of gastrointestinal motility encompasses techniques like manometry of the esophagus and/or antro duodenum, Electrogastrography (EGG), radioisotopic assessment of gastric emptying, expiration testing for gastric emptying capacity, and Ultrasonography to observe gastric emptying and duodeno-gastric reflux. Computed Tomography (CT) scan and EGG may help rule out other causes of dyspeptic and reflux symptoms; experts also recommend duodenal biopsy, fundic accommodation tests, and evaluation of duodenal hypersensitivity to identify specific pathologies in rare situations.

Table 1 — *Alarm symptoms to investigate in patients with dyspepsia*[7,13]

■ Age >45 years (in areas with a high prevalence of gastric cancer: >37 years)*
■ Recurrent vomiting
■ Weight loss
■ Dysphagia
■ Evidence of GI bleeding
■ Family history of cancer
■ Hematemesis, Melena*
■ New onset dyspepsia in the 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, respectively.

**Opinion of the experts*

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In Asia, where gastric cancer is more common and occurs at a younger age, relying solely on *H. pylori* eradication without endoscopy may risk missing malignancies. Early upper GI endoscopy is recommended for dyspeptic patients over 40 to exclude organic causes, including gastric cancer[2].

Experts noted that *H. pylori* can be assessed via Rapid Urease Tests (RUT) or gastric/duodenal biopsies, though RUT has limited validation. The C^{13} breath test is costly and scarce in India, while the C^{14} test is banned due to radiation risks. Experts recommend endoscopy and *H. pylori* testing if alarm symptoms are present or initial therapy fails, to identify and treat any underlying organic cause.

Management of FD-GERD

The comprehensive management of GERD and FD overlap requires both pharmacological therapy and lifestyle modifications to address risk factors[1,3].

Acid-suppressing and neutralizing agents :

Acid-suppressing agents such as PPIs, are very commonly given empirically in patients with GERD, on account of their very low toxicity profile and good efficacy for suppressing gastric acid secretion and symptom relief. However, the coexistence of FD or IBS and the absence of esophagitis or the presence of FGIDs is linked with diminished response or PPI failure in patients with GERD. The effectiveness of H2RAs in treating FD is debatable and are not the preferred initial choice for FD treatment, still commonly used in case of PPI failure[11]. There is also empirical evidence supporting the potential amelioration of GERD-related symptoms with alginate-based treatments[3].

Prokinetics :

Prokinetic agents comprise a diverse group of compounds that target various receptors, such as 5-hydroxytryptamine 4 (5-HT4) receptor agonists, Dopamine2 (D2) receptor antagonists, and motilin and ghrelin receptor agonists. They are suggested to alleviate symptoms of GERD by boosting esophageal motility and facilitating gastric emptying[12]. Prokinetics, when used alongside PPIs, contribute to a decrease in reflux episodes, resulting in a more significant improvement in symptom scores and a potential enhancement in patients' Quality of Life[13]. Itopride, a D2 antagonist possessing anticholinesterase properties, expedites gastric emptying by its dual mechanisms of action, targeting both dopaminergic and acetylcholinesterase pathways. Typically used in patients with FD, it has demonstrated notable effectiveness in addressing sensations of postprandial fullness and early satiety. The therapeutic benefits of itopride may stem from its effects on brain-gut communication, visceral hypersensitivity, gastric accommodation, distension-induced adaptation, and TLESRs[12] Shankar, *et al* in their survey found that approximately 80% of participating Indian Physicians reported highly favorable effectiveness of itopride, and 81.5% expressed similar sentiments regarding its safety. Furthermore, a notable 88.4% of Physicians utilize a once-daily sustained-release formulation of itopride[6]. Itopride was found comparable in efficacy to domperidone in relieving symptoms and was devoid of cardiac side effects[14]. For patients with non-ulcer dyspepsia, a study reported higher complete symptomatic relief rates with itopride (81%) compared to domperidone (70%). In another study, itopride demonstrated significantly greater moderate to complete symptomatic relief (90%) in comparison to levosulpiride (83.3%) in patients with non-ulcer dyspepsia (p=0.0146). Among the array of prokinetics utilized for FD, itopride emerges as a preferable choice, particularly for vulnerable populations like the elderly and individuals with diabetes[13]. It produces no undesirable cardiac effects due to its lack of affinity for the 5-HT4 receptors in the heart and no hyperprolactinemia[15]. The pronounced polarity of itopride hinders its ability to penetrate the blood-brain barrier, rendering it free from Central Nervous System (CNS) side effects. This characteristic establishes itopride as a safer choice compared to alternative prokinetics. Furthermore, the pharmacokinetic profile of itopride is such that it does not have any drug-drug interactions with CYP450 enzyme inhibitors, such as macrolides and azole antifungals, enabling concurrent administration with these medications[16]. As per the consensus guidelines from the Association of Physicians of India-Indian Society of Gastroenterology (API-ISG), individuals dealing with both GERD and overlapping symptoms of FD, including volume reflux and signs of delayed gastric emptying, could potentially find value in incorporating prokinetic medications into their treatment. In a recent meta-analysis of nine placebo-controlled trials involving 2,620 individuals with FD, itopride (1,372 subjects) was compared to domperidone, mosapride, or placebo (1,248 subjects). The itopride group reported significant improvements in PDS Relative Ratio (RR): 1.21; 95% Confidence Interval (CI): 1.03-1.44; p=0.02), early satiation (RR: 1.24; 95% CI: 1.01-1.53; p=0.04), and Global patient assessment scores (RR: 1.11; 95% CI: 1.03-1.19;

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p=0.006) compared to the Control group[6].

The experts agreed that itopride improves gastrointestinal motility in FD and that it is efficacious and well tolerated[17]. Among other prokinetics, the experts advised caution with the use of levosulpiride and suggested counselling of patients and follow-up to check for extrapyramidal side effects, especially in older populations and those with a positive family history of Parkinsonism.

In patients without alarm symptoms, experts suggest initiating PPI and prokinetic therapy for 4 weeks to manage suspected FD-GERD overlap[1]. If symptoms persist, further evaluation is needed[3]. With normal endoscopy, empirical PPI therapy and lifestyle changes are recommended. Persistent symptoms despite high-dose PPI may indicate refractory GERD, requiring manometry, pH monitoring, and possibly EGG or gastric scintigraphy[18-20] (Fig 1).

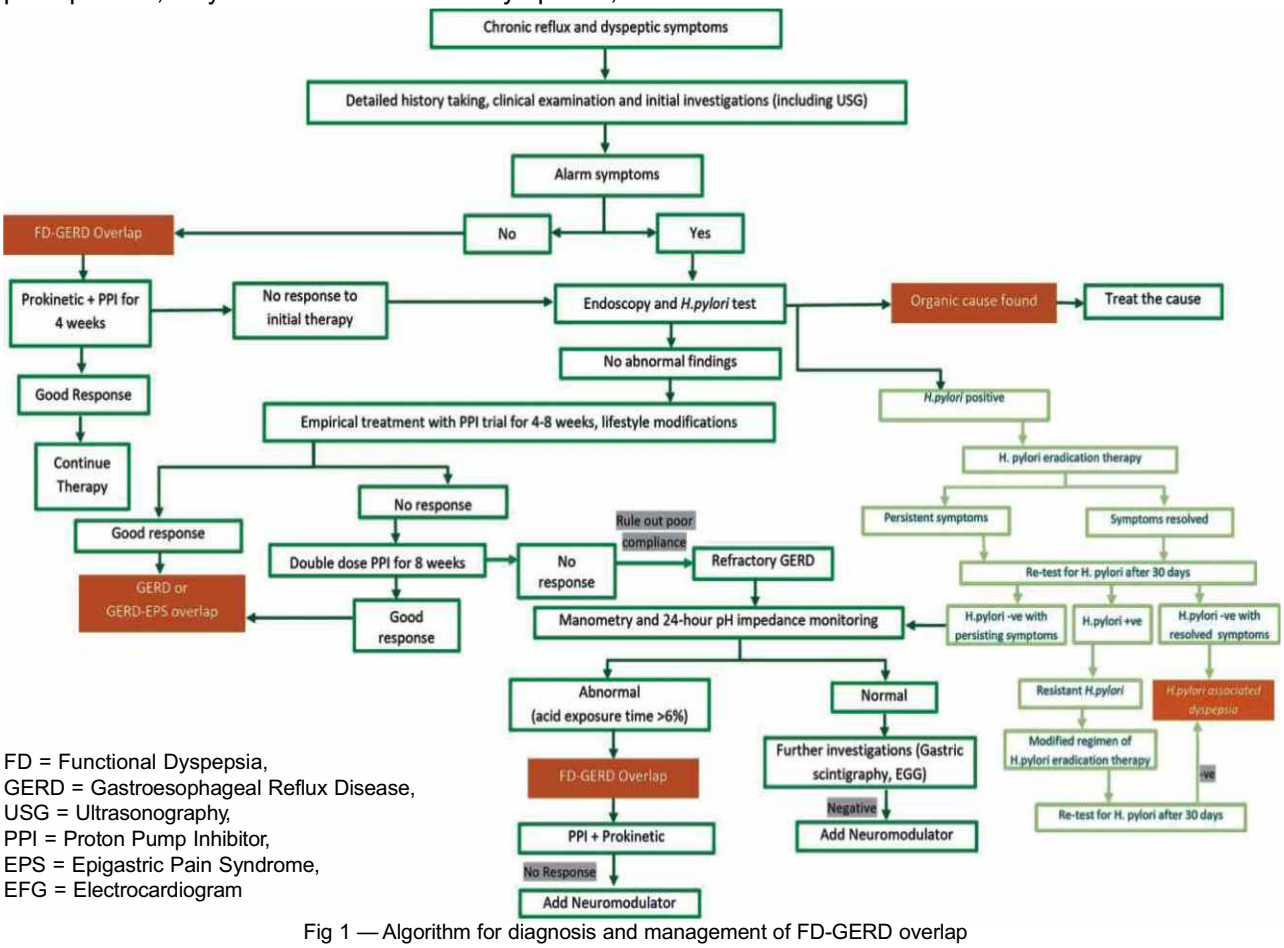
Neuromodulators :

Amitriptyline, especially when combined with pantoprazole, may relieve FD and GERD symptoms, including ulcer-like pain, bloating, and impaired gastric accommodation[10]. Experts suggested adding neuromodulators such as amitriptyline, mirtazapine, SSRIs, or SNRIs, if there is no response to PPIs and prokinetics or if EGG and scintigraphy are negative.The various treatment options are listed in Table 2.

Table 2 — Treatment options for patients with FD-GERD overlap

Acid suppressing and neutralizing therapies	Proton pump inhibitors and PCABs H2 receptor antagonist (H2RAs) Alginates, antacids and sucralfate	
Prokinetics	Idopride Cinitapride Acotiamide^ Baclofen^	Domperidone Levosulpirid* Prucalopride Metoclopramide
Neuromodulators	Amitriptyline Mirtazapine Selective Serotonin Reupake Inhibitors (SSRIs) Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs)	

^Useful for fundus relaxation/PDS type of FD only.
*Caution is advised with the use of levosulpiride. Counsel patient and follow-up to check for extrapyramidal side effects, especially in older population.



FD = Functional Dyspepsia,
GERD = Gastroesophageal Reflux Disease,
USG = Ultrasonography,
PPI = Proton Pump Inhibitor,
EPS = Epigastric Pain Syndrome,
EFG = Electrocardiogram

Fig 1 — Algorithm for diagnosis and management of FD-GERD overlap

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Proposed Algorithm for the Diagnosis and Management of FD-GERD Overlap :

The expert consensus algorithm for diagnosing and managing FD-GERD overlap, shown in Fig 1, outlines a systematic approach for patients with chronic reflux and dyspeptic symptoms. It emphasizes thorough initial evaluation, identification of alarm symptoms, and key investigations such as upper GI endoscopy, *H. pylori* testing, esophageal manometry, and 24-hour pH impedance monitoring, to help in the diagnosis of FD-GERD overlap. Given the high prevalence of *H. pylori* in India, eradication therapy is included for *H. pylori*-positive patients. In the absence of endoscopic abnormalities, empirical treatment with PPIs, prokinetics, and neuromodulators is recommended based on symptom profile.

Conclusion :

The significant convergence between two distinct conditions, FD and GERD, poses several challenges in terms of diagnosis and treatment. Indian research focusing on FD, GERD and conditions that exhibit overlapping symptoms is scarce, leading to reliance on data from clinical studies with Western populations. In the Indian population, the complex interplay of cultural, physiological, infectious, dietary, genetic and environmental factors presents unique challenges in managing the overlap between FD and GERD. The experts aimed to bring out a comprehensive approach for accurate diagnosis and specific interventions involved in the management of FD-GERD overlap. The consolidated views and recommendations from these Indian experts are expected to guide Clinicians in reducing the socioeconomic impact of FD-GERD overlap in India.

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