API-ISG Consensus Guidelines for Management of Gastro-oesophageal Reflux Disease

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Abstract
Gastroesophageal reflux disease (GERD) is a common problem in the community. The Indian Society of Gastroenterology and Association of Physicians of India have developed this evidence-based practice guideline for management of GERD in adults. A modified Delphi process was used to develop this consensus containing 43 statements, which were generated by electronic voting iteration as well as face-to-face meeting, and review of the supporting literature primarily from India. These statements include 4 on epidemiology, 9 on clinical presentation, 11 on investigations, 18 on treatment (including medical, endoscopic, and surgical modalities), and one on complications of GERD. The statement was regarded as accepted when the proportion of those who voted either to accept completely or with minor reservation was 80% or higher. The prevalence of GERD in large population-based studies in India is approximately 10% and is probably increasing due to lifestyle changes and increase in obesity. The diagnosis of GERD in the community should be mainly based on presence of classical symptoms like heartburn and sour regurgitation, and empiric treatment with a proton pump inhibitor (PPI) or H2 receptor antagonist should be given. All PPIs in equipotent doses are similar in their efficacy in the management of symptoms. Patients in whom symptoms do not respond adequately to PPI are regarded as having PPI-refractory GERD. Invasive investigations should be limited to patients with alarm symptoms and those with refractory GERD.

Introduction
The prevalence of gastroesophageal reflux disease (GERD) is around 8-12%.1-3 There is heterogeneity in the practice and availability of technology throughout our country with unavailability of standardised guidelines for GERD. These guidelines are made through a collaborative effort of The Indian Society of Gastroenterology (ISG) and Association of Physicians of India (API). A set of consensus statements relevant for the diagnosis and management of GERD in India have been complied.

Methods
A modified Delphi process6 was adopted to develop consensus statements for the diagnosis and management of GERD in India. Seven areas were identified, namely, epidemiology, clinical presentation, diagnosis and investigations, medical treatment, surgical and endoscopic management and complications.

An initial list of statements was generated and circulated to the Task Force members. The first vote was conducted by Survey-Monkey, without explanation or justification for the statements. Feedback regarding the statements was collated and modifications made where appropriate. Literature on GERD, both Indian and international, was then collated and copies were circulated to all the members online via Dropbox. The literature included all accessible Indian and International (original papers and abstracts) articles and guidelines on GERD. The members voted again on the statements by email after reviewing the literature. The results of the second vote were collated. Finally, the Task Force members met in Delhi and discussed the 48 statements developed based on feedback from the two rounds of votes. All relevant available literature was reviewed, with emphasis on Indian data, whenever available.

The third vote followed these presentations, and was captured using electronic vote pads. The options given for each statement were (A) accept completely, (B) accept with some reservation, (C) accept with major reservation, (D) reject with reservation, and (E) reject completely. Consensus on a statement was considered achieved when 80% or more of the voting members chose to “accept completely” or “accept with some reservation” the statement. A statement was considered refuted when 80% or more of the voting members indicated “reject completely” or “reject with some reservation.” When no consensus was reached on a particular statement, it was modified,
and a further vote was sought. If this vote too remained inconclusive, the statement was either deleted or modified according to the discussion. A total of 43 statements were accepted and the rest were deleted. The participants were then asked to grade the level of evidence available and the strength of recommendation for the accepted statements, using a modification of the scheme suggested by the Canadian Task Force on the Periodic Health Examination (Table 1).  

A total of 10 experts from ISG and 6 experts from API were part of the committee for formulation and discussion of the statements.

**GERD: Epidemiology**

1. Gastroesophageal reflux disease is defined as reflux of gastric content into the esophagus, resulting in significant symptoms and/or complications

Voting percentage: A 91.6, D 8.3

Level of evidence: III

Grade of recommendation: III

The term gastroesophageal reflux denotes retrograde movement of gastric content into the esophagus. Although mild, occasional reflux of gastric content into esophagus is common, it is considered a disease if it is significant enough to cause symptoms and/or complications. Sour regurgitation and heartburn are the cardinal symptoms of GERD. Accordingly, the reflux of gastric content into esophagus, resulting in symptom sometimes (heartburn/regurgitation for at least once a week for at least one month) and/or complications was considered as an appropriate definition of GERD by the task force. The complications of GERD are discussed later in this guideline. The multicenter study on epidemiology of GERD in India used symptoms for the definition of GERD. The addition of complications makes the definition more comprehensive.

2. GERD is common in India, in both urban and rural population.

Voting percentage: A 92.3, B 7.6

Level of evidence: II-2

Grade of recommendation: B

Globally, prevalence of GERD is estimated to be around 15%. The overall prevalence in Asia is reported to be lower but there are regional variations and India is among the nations with higher prevalence. Data from both community and hospital based studies suggest that GERD is common in India irrespective of geographical or rural/urban location. Among the three community based studies, the largest one was from Vellore, Tamil Nadu. It included 6174 subjects (Rural – 3017, Urban – 3157) and prevalence of GERD was 8.2%. The prevalence in rural area was 5.07% and in urban area was 11.1%. Another community based study from Trivandrum, Kerala (n=1072) found a higher prevalence of GERD (22.2%). The prevalence in urban area was 29% and 19% in rural area. The third population based study was from Ladakh where the prevalence in rural area was higher (23%) compared to urban area (13.1%). The overall prevalence was 18.7%.

In addition to the community based studies, there are several studies from India. The ISG task force on GERD conducted a study where data were collected from different parts of the country. This prospective multicenter study included 11 urban areas, 2 rural areas and 2 slums. The prevalence of GERD was 7.6% among the 3224 participants (southern India 8.35 % vs northern India 6.74 % [p=ns]). The prevalence figures from hospital based studies have ranged from 15-30%. Overall, these data suggest that GERD is a common problem in India with the disease burden similar to the figures from the west.

3. The risk factors for GERD include obesity, smoking, increase in intra-abdominal pressure and certain dietary factors.

Voting percentage: A 92.3, B 7.6

Level of evidence: II-2

Grade of recommendation: B

Multiple dietary and lifestyle factors have been implicated as risk factors for GERD. The associations with most of these factors except for obesity have been weak or inconsistent. Obesity has a detrimental effect on the barrier function of gastroesophageal junction and also results in increased intra-abdominal pressure. There is a direct association of waist circumference and application of abdominal belt with increased intra-gastric pressure. This in turn results in more frequent gastroesophageal reflux. Both the community-based studies from South India showed a higher risk of GERD with BMI >25. Meta-analysis of global data has shown an OR of 2.16 (2.05-2.28) for GERD in obese individuals.

Smoking and consumption of tobacco has been linked with GERD. The results from the recent meta-analysis of 30 studies show an OR of 1.26 (1.04-1.52) with smoking. As smoking is not protective and considering other health hazards associated with it, it may be prudent to advice against tobacco consumption or smoking. Existing data from India and from meta-analysis of global data does not support alcohol as a risk factor for GERD.

Dietary factors are often considered as a trigger for reflux symptoms but data supporting this is weak. As there are many items in the diet, studying the effect of individual factors is challenging. Some of the studies from India that meat consumption was associated with GERD symptoms. The evidence for tea, coffee and aerated beverages as a trigger for GERD are not conclusive and a meta-analysis showed no association of GERD with coffee intake. However, patients who are able to identify a clear association of reflux symptoms with specific dietary items may benefit from restricting their intake.

4. There is an inverse association between Helicobacter pylori infection and GERD.
Voting percentage: A 84.6, B 15.3
Level of evidence: II-2
Grade of recommendation: B

H pylori infection occurs in the gastric mucosa; a number of studies have investigated the association of H. pylori and GERD. The results of two meta-analysis have been conflicting. A large prospective cohort study form Korea looked at the effect of H pylori eradication in a healthy population undergoing screening for this infection. The prevalence of reflux esophagitis was almost twice in the non-infected group compared to the group with infection (6.4% vs. 3.3%, p < 0.001). On follow up of the subjects with H pylori infection after eradication therapy, the prevalence of GERD increased in those with successful eradication of the bacteria compared to those with persistent infection. Based on data from Asian countries, H pylori infection appears to have negative association with GERD but this needs to be investigated in the Indian population.

**GERD Symptomatology**

5. GERD can have both esophageal and extra-esophageal symptoms.

Voting percentage: A 92.3, B 7.6
Level of evidence: II-2
Grade of recommendation: A

“Montreal definition and classifications” divided symptoms of GERD into esophageal syndrome and extraesophageal syndrome. The esophageal syndromes were further classified into symptomatic syndromes or syndromes with esophageal injury. The extra-esophageal syndromes were further classified into those with established associations (reflux-cough, reflux-laryngitis, reflux-asthma, and reflux-dental erosion syndromes) and those with proposed associations (pharyngitis, sinusitis, idiopathic pulmonary fibrosis, and recurrent otitis media) of the occurrence of extraesophageal symptoms can be explained by two plausible mechanisms -1) reflux theory and 2) reflex theory.

There is a paucity of prevalence studies from Asia on extraesophageal symptoms of GERD. A systematic review from population based studies from Asia showed GERD was prevalent in 11-65% patients with extraesophageal symptoms (asthma, dental erosions, ENT symptoms and chronic laryngitis). A multicentre study (12 centres) by ISG task force showed presence of nocturnal cough (15.5% vs 2.9%, p=0.001) and hoarseness of voice (6.1% vs 0.9%, p=0.0001) was higher in patients with GERD than with no GERD symptoms.

Thus, GERD may present with both esophageal and extraesophageal symptoms. However, extraesophageal symptoms rarely occur in isolation without typical symptoms of GERD.

6. The cardinal symptoms of GERD are heartburn and sour regurgitation.

Voting percentage: A 92.3, B 7.6
Level of evidence: II-1
Grade of recommendation: A

Heartburn is defined as a burning sensation in the retrosternal area, and sour regurgitation is defined as the perception of flow of refluxed gastric content into the mouth or hypopharynx. Heartburn and regurgitations are the typical and predominant symptoms of GERD. A clinical diagnosis of GERD can be made on the basis of history alone with sensitivity and specificity of 67% and 70%, respectively.

7. Approximately 30-50% of patients with GERD have additional symptoms of functional dyspepsia.

Voting percentage: A 100, B
Level of evidence: II-2
Grade of recommendation: A

Functional dyspepsia is a functional GI disorder defined by the presence of one or more of these dyspeptic symptoms- post prandial fullness, early satiety, epigastric pain and epigastric burning.

The overlap between GERD and functional dyspepsia can be explained by the similar pathogenic mechanism - dysmotility or visceral hypersensitivity. Heartburn, regurgitation, and chest pain are typical GERD symptoms originating from reflux-related sensory stimulation of the esophageal mucosa, while belching, epigastric pain, and epigastric burning appear to be dyspeptic symptoms that might arise from the distal esophagus. A systematic review showed that dyspeptic symptoms were present in more than one third of subjects with GERD.

The ISG Task Force study reported that abdominal pain was present in 34.3%, difficulty in passing stool in 21.7%, and mucus in stool in 9% of patients with GERD, which was higher than in the no-GERD group (8%, 6.7% and 3.5%, respectively). Shah et al found that the prevalence of heartburn (34.6% vs 2.8%) and regurgitation (17.9% vs 1.5%) was higher in subjects with dyspepsia as compared to those with no dyspepsia.

Thus, overlap between functional GI disorder and GERD is common and early identification is mandatory for future treatment implication.

8. The alarm symptoms in patients with GERD include dysphagia, odynophagia, GI bleeding, weight loss, anaemia and new onset symptoms in age > 55 years.

Voting percentage: A 100
Level of evidence: II-2
Grade of recommendation: A

Alarm features in GERD are dysphagia, odynophagia, GI bleeding, iron deficiency anaemia, progressive weight loss, and new onset of atypical symptoms at age 45-55 years. Erosive reflux esophagitis may cause upper GI bleeding, odynophagia and dysphagia. In ISG task force multicenter study, 4.1% with GERD had previous hematemes.

In a patient with dysphagia motility disorder, rings, peptic sticture and malignancy should be ruled out. As result of widespread use of PPI, GERD complications have drastically reduced. GERD is an independent risk factor for esophageal malignancy. UGI endoscopy is advocated subjects with heartburn associated with alarm symptoms, and in elderly patients with new onset of GERD symptoms.

9. The extra-esophageal symptoms of GERD include chronic cough, asthma, chronic laryngitis, and globus symptoms.

Voting percentage: A 100
Level of evidence: II-2
Grade of recommendation: A

Extraesophageal symptoms are not uncommon in GERD patients. Four syndromes (reflux cough, reflux laryngitis, reflux asthma, and reflux dental erosions) have been found to be associated with GERD. Temporal association between cough and reflux was established with 24-hour ambulatory acoustic cough monitoring with simultaneous impedance/pH monitoring technique. A population based Chinese study reported that
extra-esophageal symptoms including snoring (28% vs 12%), laryngitis (23.7% vs 11.8%), globus sensation (23.7% vs 5%), asthma (6.5% vs 2.2%), bronchitis (15.4% vs 8.9%) and chronic cough (21.4% vs 11%) was higher in patients with symptomatic GERD than in those with no GERD symptoms. Reflux laryngitis may lead to hoarseness, dysphonia, burning throat, excessive throat clearing, chronic cough, globus sensation, laryngospasm, postnasal drip and dysphagia. However, it is important to note that most patients with extra-esophageal symptoms also have symptomatic GERD.

10. Patients with difficult to treat non-seasonal asthma and chronic cough should be evaluated for GERD.

Voting percentage: A 100
Level of evidence: II-2
Grade of recommendation: B

Almost one third of asthmatic patients have GERD. GER may not only worsen during an episode of airways obstruction, but also may serve as a trigger for an asthmatic attack by causing bronchospasm. Patients with reflux-associated asthma may manifest with typical symptoms of GER, but approximately 25 to 30% have clinically silent reflux. Studies from India have shown that GERD was prevalent in 50-70% asthmatics, and that addition of PPI improved pulmonary function test in patients with difficult to treat asthma and GERD.

There appears to be a temporal relationship between chronic cough and reflux in 30-48% of patients. In the ISG task force study, 15.5% GERD subjects had nocturnal cough compared to with 2.9% no GERD subjects. A survey of 500 physicians from India reported that 10.4% of their patients with chronic cough had cough related to GERD. About 80% of the physicians treated these empirically with PPI. However response of chronic cough to PPI is not consistent. In 9 studies comparing PPI to placebo, prolonged PPI therapy (2-3 months) did not have significant improvement over placebo in resolution of cough (odds ratio 0.46: 95% CI 0.19-1.15). Nevertheless, PPI trial is recommended in chronic cough patients with typical symptoms of GERD.

11. Non-cardiac chest pain can be a manifestation of GERD.

Voting percentage: A 100
Level of evidence: II-2
Grade of recommendation: A

Non-cardiac chest pain (NCCP) is defined as recurrent episodes of angina-like retrosternal chest pain in the absence of cardiac abnormalities. Gastroesophageal reflux disease (GERD), esophageal motility disorders and functional chest pain (visceral or central hypersensitivity) are the main underlying mechanisms for NCCP. GERD is seen in 25-60% of patients with NCCP; 10-70% of patients have erosive esophagitis, and abnormal acid exposure is seen in 50-60% patients.

Jain et al showed that 49% of patients with NCCP had erosive esophagitis, and 85% responded to 2 weeks of PPI therapy. The chest pain in patients with abnormal esophageal acid exposure and/or reflux esophagitis tends to respond to PPI treatment, whereas patients without objective evidence of GERD have little or no response. It is advocated to do endoscopy and ambulatory pH monitoring in patients with NCCP who fail to respond to trial with PPI therapy.

12. Symptoms of GERD can lead to sleep disturbance.

Voting percentage: A 100
Level of evidence: II-1
Grade of recommendation: A

Nocturnal symptoms in GERD are common and associated with sleep disturbance. Mechanisms responsible for night time reflux include delayed gastric emptying, reduced esophageal peristalsis, decrease in swallowing and salivary secretion, delayed esophageal clearance during sleep, and heightened sensory perception. In nationwide telephone survey of 1000 adults with GERD, 79% reported night-time heartburn, 75% had sleep disturbances and 71% using over-the-counter medications. In systematic review of 59 studies, nocturnal symptoms was prevalent in 54% ± 22% of subjects. In a study from Kerala, 10.2% of subjects had nocturnal symptoms of GERD. Thus, nocturnal symptoms are common, and adversely affects the quality of life in subjects with GERD.

13. GERD may adversely affect quality of life.

Voting percentage: A 100
Level of evidence: II-2
Grade of recommendation: B

Disease severity and non-disease factor (anxiety, depression) both are strongly correlated with impaired health related quality of life (QoL). To assess QoL in GERD various survey/instruments have been used. Few of them are generic (SF-36, Euro QoL) and some are disease specific (GERQ,GORD-HRQoL, HBQoL). In a systematic review of 19 studies, patients with severe GERD scored lower for physical and mental health, as well as psychological and general well-being. Absenteeism from work was also higher among patients with severe GERD. A systematic review of 19 studies showed patients with persistent symptoms despite of PPI scored 8–16% lower for physical health and 2–12% lower for mental health compared to those who responded. Nocturnal GERD have a significant negative impact on sleep and well-being. In another study, higher severity of symptoms, sleep abnormalities and work loss were more common among GERD patients with nocturnal symptoms. There are no data from India on QoL in GERD patients.

Investigations

14. The clinical diagnosis of GERD is based on symptoms (heartburn and/or sour regurgitation) and investigations are necessary in only a few patients.

Voting percentage: A 100
Level of evidence: II-1
Grade of recommendation: A

The cardinal symptoms of GERD are heartburn and sour regurgitation. The use of a symptom based questionnaire has a sensitivity and specificity of 62% and 67%, respectively. In a meta-analysis the accuracy for a symptom based diagnosis by a primary care physician was comparable to that made by a specialist. Investigations to diagnose GERD, such as endoscopy, 24-h impedance pH-metry, are required only when initial treatment fails, or prior to surgery.

15. Positive response to PPI challenge may be used for confirmation of GERD in the community.

Voting percentage: A 92.3, B 7.6
Level of evidence: I
Grade of recommendation: A

A “PPI challenge” is a test where a PPI is given to patients with a
presumptive diagnosis of GERD to assess the response to treatment. A rapid symptomatic improvement is considered “positive response” and commonly used to validate the diagnosis of GERD. Empirical therapy with PPI is considered useful and simple diagnostic tool to identify patients with GERD. A meta-analysis of 8 studies showed pooled sensitivity and specificity for PPI test was 80% and 74%, respectively. The optimal duration, dose and selection of the PPI varies across studies with most using standard (single) dose for 7 to 14 days. It is an inexpensive and easy to administer test. Its limitation is a poor specificity and hence a negative PPI challenge does not rule out GERD. The PPI challenge must be used only in patients without any warning signs.

16. Patients with GERD and alarm symptoms should be referred for a prompt upper gastrointestinal endoscopy.

Voting percentage: A 100
Level of evidence: II-2
Grade of recommendation: A

The alarm symptoms in patients with GERD include dysphagia, odynophagia, GI bleeding, weight loss, anaemia and new onset symptom in age > 55 years. These alarm symptoms are present in upto 10% of the patients with GERD. In a prospective study, endoscopy in patients with GERD and alarm symptoms influenced the overall management in 40% of the patients, mainly by dilating esophageal strictures, finding Barrett’s oesophagus, or detecting severe esophagitis. In a meta-analysis, the sensitivity of individual alarm symptoms for detection of GI malignancy was between 9 to 41%, but the pooled sensitivity, specificity, positive and negative predictive values for “any alarm symptom” were 75%, 79%, 5.9% and 99.4% respectively. The majority of endoscopies in patients with alarm symptoms are normal or show minor disease, leading to a low sensitivity.

17. Patients with GERD, especially those with long standing symptoms should be considered for upper gastrointestinal endoscopy.

Voting percentage: A 92.3, B 7.6
Level of evidence: III
Grade of recommendation: C

Upper GI endoscopy should be done to determine whether the patient has endoscopic reflux disease, the grade of GERD, and the presence of hiatus hernia and its type and size, complications such as peptic stricture and Barrett’s esophagus, and for histologic presence of dysplasia. Patients with long standing GERD may have a higher prevalence of complications. Although there is no literature to support this practice, the core committee felt that an endoscopy will help in optimizing the management of these patients.

18. Patients with GERD undergoing endoscopy should be evaluated for grade of esophagitis, hiatus hernia and Barrett’s esophagus.

Voting percentage: A 100
Level of evidence: II-1
Grade of recommendation: A

Esophagitis is the presence of mucosal breaks on endoscopy. The severity of esophagitis is graded by the Los Angeles (LA) classification system on endoscopy. The grading is from A to D and represents mild to severe erosions. Esophagitis is seen at endoscopy in only 8.8% of Indian patients of GERD. The grade of esophagitis has important bearing on treatment, patient response, complications and prognosis. Patients with higher grade of esophagitis may have more severe symptoms, respond better to PPI as compared to H2RA, require longer duration of treatment with PPI, and have higher prevalence of esophageal motility disorders.

The displacement of a part of the stomach through the esophageal hiatus of the diaphragm is known as hiatal hernia. Hiatus hernia alters the integrity of the gastroesophageal junction and predisposes to reflux. In a study from India, the presence of a hiatus hernia was associated with GERD (odds ratio 6.93 [95% confidence interval, 2.58-18.5]). Hiatus hernia is more often present in severe esophagitis (70%) as compared to mild esophagitis (22%). A hiatus hernia also predisposes to formation of an ‘acid pocket’, which serves as a reservoir for acid reflux. Barrett’s esophagus is the condition in which an abnormal columnar epithelium replaces the stratified squamous epithelium that normally lines the distal esophagus. There are no data on prevalence of Barrett’s esophagus in patients with GERD in India. A tertiary hospital based study has reported a frequency 16%. The abnormal columnar epithelium is predisposed to malignancy, with an annual risk of progression to cancer of 0.12% for non dysplastic Barrett’s and upto 13.4% for confirmed high grade dysplasia.

19. A proportion of patients with GERD, especially those who respond poorly to proton-pump inhibitors (PPI) or have dysphagia, should be evaluated for eosinophilic esophagitis.

Voting percentage: A 92.3, B 7.6
Level of evidence: II-3
Grade of recommendation: B

Eosinophilic esophagitis represents a chronic antigen mediated esophageal disease characterized clinically by symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation. Symptoms of eosinophilic esophagitis can mimic those of GERD; additional symptoms of dysphagia and food bolus impaction are more often present in eosinophilic esophagitis. There are no data on population based prevalence of eosinophilic esophagitis in India. In a hospital based study from northern India, of 185 consecutive patients with GERD, 3.2% had eosinophilic esophagitis. On multivariate analysis, a history of allergy (OR 11.6 [95% CI 1.5-90.1, p=0.01]), and non-response to PPI (OR 0.04 [95% CI 0.004-0.48, p=0.01]) were predictors of eosinophilic esophagitis. Therefore, it is important to consider this entity in refractory gastroesophageal reflux symptoms.

20. Symptoms of GERD do not necessarily correlate with endoscopic severity of GERD.

Voting percentage: A 100
Level of evidence: II-2
Grade of recommendation: A

GERD-symptom based score of patients with non-erotic, mild erosive and severe erosive esophagitis are similar. Elderly patients, and those with Barrett’s esophagus complain of less symptoms despite severe degree of endoscopic esophagitis. In contrast, patients with non-erotic GERD complain of significant heartburn, as esophageal hypersensitivity is a major determinant of symptoms. For this reason, in the Rome IV criteria, a new subgroup of patients with
Reflux hypersensitivity and functional heartburn have been recognized.21

21. A) Barium esophagogram has limited role in diagnosis of patients with GERD
Voting percentage: A 100
Level of evidence: II-2
Grade of recommendation: A

21. B) Radionuclide Scintigraphy has limited role in diagnosis of patients with GERD
Voting percentage: A 100
Level of evidence: II-2
Grade of recommendation: B

Barium swallow can detect spontaneous gastroesophageal reflux or it can be provoked by manoeuvres. It may also detect esophageal strictures and hiatus hernia. However, barium swallow has a low sensitivity (67%) and specificity (47%) to identify GERD.72 Hence, barium studies are not of value in diagnosis of GERD.73

In radionuclide scintigraphy, a radiolabeled colloid is administered orally and followed by a gamma camera to detect reflux episodes. It is commonly used for children due to its non-invasive nature and a relatively low radiation dose. In various studies, the diagnostic accuracy of radionuclide scintigraphy for GERD were very low.74,75 The testing in scintigraphy lasts for only few hours compared to 24 hour recording with a pH probe. The joint North American and European guidelines for paediatric GERD also recommend against the use of scintigraphy for the diagnosis of GERD.76

22. Patients not responding with PPI should be referred for further evaluation including UGI endoscopy and 24-hr pH monitoring.
Voting percentage: A 100
Level of evidence: II-2
Grade of recommendation: A

The causes of PPI failure include non-compliance to treatment, ongoing acidic reflux, weak acidic or alkaline reflux, reflux hypersensitivity and functional heartburn. The role of endoscopy in patients not responding with PPI is to demonstrate erosive esophagitis, rule out alternative diagnosis like eosinophilic esophagitis and to diagnose complications like peptic stricture or Barrett’s esophagus.

Ambulatory reflux monitoring involves insertion of a pH probe 5 cm above the lower esophageal sphincter and recording the pH exposure data for 24 hours continuously. A fall in pH to <4 from a baseline pH of 7 is considered as an acid reflux.77 Reflux monitoring demonstrates evidence of excessive esophageal acid exposure time (AET) and an abnormal number of reflux events; adding impedance allows measurement of nonacid reflux events, and association between symptoms and reflux events. Symptom index (SI) and symptom association probability (SAP) are useful to differentiate reflux hypersensitivity from functional heartburn. An AET of 4% is definitively normal (physiological) and >6% can be considered definitively abnormal.77 A total of >80 reflux episodes per 24 hours is considered as definitively abnormal, while a number <40 is physiological.77

Thus, a combination of endoscopy and 24-hr pH with impedance testing can help to confirm GERD, provide alternative diagnosis and further characterize patients and help in the optimal management of these patients.

23. While a 24-hpH monitoring is the gold standard for diagnosis of GERD currently, this test is required only a few select subjects.
Voting percentage: A 100
Level of evidence: II-2
Grade of recommendation: A

The 24-h impedance pH monitoring is the current gold standard for detection of reflux episodes as impedence can detect anterograde and retrograde bolus (gas, liquid and mixed) flow along with chemical characterization of the refluxate.77

The sensitivity and specificity of 24-hour pH study is 77-100% and 85-100%, respectively for discrimination of esophagitis from normal controls.77 Amongst six diagnostic tests to detect GERD (omeprazole challenge, endoscopy, esophageal histology, barium swallow, scintigraphy, 24-hour pH monitoring),35 pH monitoring has the highest diagnostic accuracy (82.2%).

The current indications for 24-hour pH monitoring include the following:77

a) Refractory GERD: to determine if there is ongoing acid reflux, symptomatic non acidic reflux or no reflux; b) Atypical symptoms; and c) Prior to anti-reflux surgery.

24. Patients with extra esophageal symptoms should undergo tests for proving the diagnosis of GERD, if they do not respond to PPI.
Voting percentage: A 83.3, B 16.7
Level of evidence: II-1
Grade of recommendation: B

The extra esophageal symptoms of GERD include reflux induced cough, asthma, laryngitis and dental erosions.8 Studies from India have reported a prevalence of GERD in about 50% of the patients of asthma,31 and a higher prevalence of 70% in patients with difficult to treat asthma.32 It is important to remember that almost 25% of patients with asthma and GERD diagnosed by 24-hour pH monitoring, do not have any symptoms of reflux.32 In a physician survey from India, 10% of patients with chronic cough were attributed to GERD clinically and 80% of these were treated empirically with PPI.34 Dental erosions were found to be present in 88% of GERD patients as compared to 32% in controls in a study from South India.79 There are no Indian studies for prevalence of laryngitis in patients with GERD, but one from Malaysia showed a GERD prevalence of 65% among patients of chronic laryngitis.79

International guidelines recommend PPI trial to treat extraesophageal symptoms in patients who also have typical symptoms of GERD, and 24-hour pH monitoring in patients who do not have typical symptoms of GERD.28 However, considering the cost and lack of widespread availability of 24-hour pH monitoring in India, the consensus of the group was to give short-term PPI to patients with extraesophageal symptoms, and investigate only if there is no improvement.

GERD treatment

25. Triggers for reflux symptoms should be identified in individual patients and if present should be avoided.
Voting percentage: A 100
Level of evidence: II-2
Grade of recommendation: C

Dietary modification for GERD is based upon evidence and presumptions that certain food items and habits may trigger reflux by altering the anti-reflux mechanisms. However, the evidence regarding food items is weak, inconsistent and controversial,
and hence, a general recommendation on avoidance of food items cannot be made.

Similarly, the relationship between caffeine, tobacco, alcohol and GERD remains heterogeneous and unclear.27,83

There is weak evidence regarding the association of food items like chocolate, citrus fruits, carbonated beverages, spicy foods, fatty foods, mint etc. with GERD symptoms. However, there are no studies which have evaluated the effect of their cessation on symptom response.45

26. Weight reduction is recommended for obese/overweight patients with GERD

Voting percentage: A 81.8, B 18.1
Level of evidence: I
Grade of recommendation: B

Elevation of the head end of bed (HOB) should decrease the reflux of acidic gastric contents in the esophagus. As compared to patients who sleep flat, those with elevated HOB have fewer and shorter reflux episodes and lesser reflux symptoms.70,93 There is also reduced esophageal acid exposure and acid clearance time in nocturnal refluxers, and improvement in heartburn and sleep.79

28. Patients of GERD should be advised not to lie down within 2 hours after a meal.

Voting percentage: A 81.8, B 18.1
Level of evidence: II-3
Grade of recommendation: C

Early meal (6 hours before bed-time) is associated with less supine reflux as compared to a late meal (2 hours before bed-time).95 Such an association is not found in healthy.96

29. Patients who have infrequent symptoms of GER may be treated with antacids and/or H2 receptor antagonists

Voting percentage: A 100
Level of evidence: I
Grade of recommendation: A

Histamine H2 receptor blockers (H2RAs) reduce acid secretion by competitively antagonizing the H2-receptors on the parietal cells. Antacids (basic aluminium, calcium, or magnesium compounds), act by neutralizing acid in the stomach; raft forming agents such as alginates create a physical barrier against reflux, and sucralfate (aluminium hydroxide and sucrose sulphate) coats the denuded mucosa in the esophagus/ proximal stomach. In a meta-analysis, that evaluated the role of over the counter (OTC) medications such as H2RAs (10 trials, 6382 patients), antacids (4 trials, 1155 patients) and alginite/ antacid combination (4 trials, 284 patients) in patients with GERD, all OTC medications were more effective than placebo in providing symptom relief.97

30. The initial standard of care of GERD is use of proton pump inhibitors for 4 weeks in standard doses.

Voting percentage: A 100
Level of evidence: I
Grade of recommendation: A

Proton pump inhibitors (PPIs) irreversibly inhibit the activated H+ K+ ATPase proton pump in the gastric parietal cells, and this effect lasts until the generation of new pumps. PPI therefore needs to be administered daily for sustained acid suppression.98 PPIs should be administered 30 – 60 minutes before a meal for optimal effects. In a Cochrane review on short term treatment of un-investigated heartburn and NERD, both PPIs and H2RAs were more effective than placebo for heartburn remission, both in the empirical treatment group [(PPIs-OR: 0.37 (2 trials, 95% CI 0.32 to 0.44)) and NERD group [(PPIs-OR: 0.71 (10 trials, 95% CI 0.65 to 0.78)].99 PPIs were also more effective than H2RAs for heartburn remission. Overall heartburn remission rates with PPIs varies from 37 – 61% in patients with NERD (placebo response: 12.6%) or un-investigated heart burn (placebo response: 25.1%) and 56 – 77% (placebo response: 7.5%) in patients with esophagitis, while healing of esophagitis occurs in 72 – 83% patients with erosive reflux disease (ERD) (placebo response: 28.3%).

The standard dose of all PPIs have been mentioned in Table 2. Patients with typical symptoms of GERD, in the absence of alarm signs such as dysphagia, odynophagia, gastrointestinal bleed, anorexia, and weight loss can be treated empirically with PPIs, and PPI trial can be considered before any diagnostic test. Further testing is indicated in patients not responding to 4 weeks of PPI therapy. In a meta-analysis of 59 RCTs (26,885 patients), symptom relief on PPIs in different groups of patients was lower in patients with uninvestigated heartburn than that in patients with ERD or confirmed NERD. Further, the response rates at 8 weeks were similar to those at 4 weeks, indicating that PPI use beyond 4 weeks does not increase the response rates.100 There is also no difference between low dose and high dose PPI therapy.101 or between once vs. twice daily PPI in terms of symptom resolution at week 4.102

31. If there is partial or no response to once daily PPI, increasing the dose of the same PPI to twice daily may be considered.

Voting percentage: A 91.6, B 8.3
Level of evidence: I
Ten to 40 percent patients with GERD have partial or no response to a standard dose of PPI.\textsuperscript{103} Given the complex pathophysiology of GERD, this group of patients is heterogeneous, comprising of patients with heart burn of other aetiologies, oesophageal dysmotility disorders, functional heartburn or functional chest pain. One third of these patients have abnormal pH test. Patients who have persistent symptoms usually have longer duration of symptoms, associated hiatus hernia, obesity, and suboptimal use of PPI. Only up to 60\% patients are adherent to treatment, and less than half the patients take PPI at appropriate time. \textsuperscript{[104]} In patients with NERD or ERD, in the absence of alarm symptoms, doubling the dose of PPI or switching to another PPI may be tried. This approach leads to an overall incremental benefit of about 20\%. \textsuperscript{105,106}

32. Patient not responding to 8 weeks of PPI in optimal dose is defined as refractory GERD.

- **Voting percentage:** A 100
- **Level of evidence:** III
- **Grade of recommendation:** C

In patients with NERD or ERD, in the absence of alarm feature, partial or no response at 4 weeks on standard dose PPI can be overcome by doubling the dose of PPI or switching to another PPI, with an overall incremental benefit of 20\%. Continuing optimal PPI therapy beyond 8 weeks will not increase the response rates, and such patients should be investigated further.

33. Patients with recurrent symptoms of GERD and refractory GERD should be referred for further evaluation.

- **Voting percentage:** A 100
- **Level of evidence:** III
- **Grade of recommendation:** C

Most patients with proven GERD develop recurrence of symptoms when PPI therapy is discontinued.\textsuperscript{107} If a patient relapses after an initial response to PPI, he should be referred for further diagnostic evaluation including an upper GI endoscopy to differentiate between ERD and NERD. This is because relapse rates are higher in patients with ERD as compared to patients with NERD. Patients with ERD may require long term PPI for symptom control and healing, while patients with NERD should be evaluated further with 24 pH-metry to prove (or disprove) GERD as their cause of symptoms. Patients in whom GERD has been excluded, other causes for symptoms including non-acid reflux, eosinophilic esophagitis,\textsuperscript{108} oesophageal dysmotility disorders, functional heartburn, and functional chest pain should be considered.\textsuperscript{108}

34. A) Presence of erosive esophagitis even after 8 weeks of PPI maybe treated with further 4-8 weeks of PPI and long term maintenance for prevention of relapse.

- **Voting percentage:** A 75, B 16.6, C 8.3
- **Level of evidence:** I
- **Grade of recommendation:** A

A meta-analysis of 43 studies (7635 patients) evaluated the speed of healing and symptomatic relief in patients with moderate to severe erosive esophagitis.\textsuperscript{109} Overall healing proportion with PPIs at 8 weeks was 83.6\% (95\% CI: 79\% - 88\%). Extending PPI beyond 8 weeks showed increment in healing from 86\% to 91\%. Therefore, extending the PPI therapy beyond 8 weeks (for 4 – 8 weeks), may have an additional incremental benefit in terms of healing.

For maintenance therapy in patients with ERD proportion of patients in remission at one year is higher (>80\%) with PPI (with or without cisapride) as compared to H2RA (49-66\%) or prokinetics (54\%).\textsuperscript{110-112} H2RAs were also superior to placebo, and could be considered in PPI intolerant patients.

B) In a patient with refractory GERD, further evaluation for alternate diagnosis and functional heartburn should be done if endoscopy is normal.

- **Voting percentage:** A 91.6, B 8.3
- **Level of evidence:** III
- **Grade of recommendation:** C

Patients with GERD symptoms, who have absence of erosions on endoscopy are labelled as having NERD; they should be further evaluated with pH-metry to rule out acid / non acid reflux as the cause of their symptoms. In patients with negative endoscopy and pH-metry, other causes of heartburn include non-acid reflux, heart burn of other etiologies like eosinophilic esophagitis, oesophageal dysmotility disorders, and functional heartburn.\textsuperscript{108}

35. Patients with non-cardiac chest pain, maybe given double daily PPI for 4 weeks, after a cardiac cause has been ruled out.

- **Voting percentage:** A 91.6, B 8.3
- **Level of evidence:** I
- **Grade of recommendation:** A

GERD is the most common cause of non-cardiac chest pain. This has led to PPI trial being used as diagnostic test for patients with reflux chest pain syndrome. The overall sensitivity and specificity of a PPI test is 80\% and 74\% respectively,\textsuperscript{106} indicating that such an approach can be used both for diagnostic and therapeutic purposes. The response to PPI is better than with placebo,\textsuperscript{113} but depends on the presence or absence of typical GERD symptoms; the therapeutic gain over placebo is 56 – 85\% in GERD positive as compared to only 0 – 17\% in GERD negative patients.\textsuperscript{39}

36. The dose of PPI should be optimized or adding H2RA at night should be considered in patients having nocturnal reflux symptoms despite use of PPI.

- **Voting percentage:** A 72.7, B 27.2
- **Level of evidence:** II-3
- **Grade of recommendation:** C

Optimizing the PPI therapy is the first strategy in patients who experience nocturnal reflux symptoms. Although single dose morning PPI achieves good day time pH and symptom control, nocturnal pH control remains inadequate in some patients. This can be improved with evening dose of PPI.\textsuperscript{114} However, even on twice-daily PPI dose, patients with GERD may experience symptoms at night, which may be due to nocturnal acid breakthrough (NAB), defined as gastric pH below 4 for more than one continuous hour at night time in subjects on PPIs.\textsuperscript{115} Addition of bed time H2RA to double dose PPI in patients with GERD decreases gastric acidity.\textsuperscript{116} However, there are concerns about tachyphylaxis associated with H2RA. Although PPI + H2RA combination reduced NAB, the effect weaned over one week, highlighting the tolerance associated with continued H2RA therapy.\textsuperscript{117}

37. A) Prokinetics have no proven role in routine management of GERD.

- **Voting percentage:** A 100
- **Level of evidence:** I
- **Grade of recommendation:** A

B) Patient with GERD having
Although prokinetics may alleviate the pathophysiology of GERD by increasing gastric and esophageal emptying, the evidence behind their clinical efficacy as add on therapy over PPI is lacking. In a RCT of 66 patients from North India, addition of mosapride to PPI was not effective in symptom control in patients with NERD, or healing in patients with ERD. In a recent meta-analysis of 12 RCTs (2403 patients), combination therapy did not have better efficacy than PPI alone for symptom control or endoscopic response, and the combination therapy was associated with worse adverse effects. A subset of patients with GERD who have delayed gastric emptying may benefit from addition of prokinetics. Given the adverse effect of many prokinetics on cardiac and neurologic function, these drugs should be used judiciously.

Baclofen, a GABA-B agonist can relieve GER by decreasing the transient LES relaxations. In a meta-analysis of 9 studies (283 patients), baclofen resulted in a short-term decrease in the number and average length of reflux episodes. For recurrence of symptoms after initial treatment in patients with uninvestigated GERD, NERD or mild erosive reflux disease, the lowest effective dose of PPI or H2RA should be advised.

After withdrawal of PPI, almost 50% patients with uninvestigated GERD remain asymptomatic over one year of follow-up. In patients with NERD, on demand therapy, but not intermittent therapy, with H2RAs or PPI provided symptom control in a proportion of patients. This approach is not useful in erosive GERD. For patients who improve on double dose PPI, stepping down to single dose for maintenance treatment can be successful in 80% patients. Overall, up to 50% patients with mild GERD/NERD will remain asymptomatic off any therapy, indicating that a definite proportion of such patients can be off therapy, and recurrences can be managed with low doses of PPI or H2RA.

39. All available PPIs in equipotent doses have similar efficacy for symptom control.

In a meta-analysis of 10 studies on 15,316 patients with erosive esophagitis, at 8 weeks there was significant but clinically modest benefit of esomeprazole over other PPIs in terms of healing (5% relative increase) and symptom control (8% relative increase). Recent network meta-analysis and systematic review showed that in equipotent doses all PPIs had similar efficacy for symptom relief in patients with NERD.

40. A) Long-term unnecessary use of PPI should be avoided.

Regurgitation rate is higher in the medication group (92% vs 85%, p=0.048). Regurgitation is significantly less in surgery group (2% vs 13%, p<0.001). Laparoscopic surgery is effective and associated with shorter hospital stay, better control of reflux symptoms and reduced risk of complications compared to open surgery.

B) The routine use of fixed dose combination therapy of PPI and prokinetics should be avoided.

Given the side effects of prokinetics and lack of evidence on their efficacy in patients with GERD, fixed dose combination of PPI and sustained release high dose prokinetic does not offer any additional advantage of PPI, in the routine management of GERD. Moreover, it increases the cost of therapy, and hence fixed dose combination of PPI and prokinetic should be avoided.

41. Patients who require long term medical management and proven GERD should be evaluated for surgery.

Anti-reflux surgeries are either in the form of fundoplication (complete or partial) which can be done by open or laparoscopic technique. The Nissen fundoplication is a complete 360° wrap, and has been replaced by partial wraps -- Dor (anterior-180°) and Toupet (posterior-270°), due to associated dysphagia and bloating with complete wrap. On long term follow up, the remission rate is higher in the medication group (esomeprazole) than the surgical group (92% vs 85%, p=0.048). Regurgitation is significantly less in surgery group (2% vs 13%, p<0.001). Laparoscopic surgery is effective and associated with shorter hospital stay, better control of reflux symptoms and reduced risk of complications compared to open surgery.

42. Endoscopic anti-reflux procedures are evolving therapeutic modalities for a select group of patients.

Endoscopic anti-reflux surgery may be considered as an alternative treatment. Anti-reflux surgery is indicated in patients with proven GERD who have failed medical management, those with volume reflux, large hiatal hernia, and complications (peptic stenosis and Barrett’s esophagus) and occasionally for extra-esophageal manifestations.

Anti-reflux surgeries are either in the form of fundoplication (complete or partial) which can be done by open or laparoscopic technique. The Nissen fundoplication is a complete 360° wrap, and has been replaced by partial wraps -- Dor (anterior-180°) and Toupet (posterior-270°), due to associated dysphagia and bloating with complete wrap. On long term follow up, the remission rate is higher in the medication group (esomeprazole) than the surgical group (92% vs 85%, p=0.048). Regurgitation is significantly less in surgery group (2% vs 13%, p<0.001). Laparoscopic surgery is effective and associated with shorter hospital stay, better control of reflux symptoms and reduced risk of complications compared to open surgery.
These endoscopic therapies include radiofrequency application (Stretta), endoscopic plication modalities (Esophyx, MUSE and GERDx) and mucosal resection techniques (anti-reflux mucosectomy). Various technique have variable response and treatment response ranges from 16%-82%. Durability of response is seen in less than 50% in long term. A systematic review of 28 studies on Stretta showed the subjective and objective improvements in health related quality of life (HRQL), heartburn score, esophageal acid exposure, and erosive esophagitis. A RCT on Stretta by Kalpala et al showed 80% had improvement in QoL compared to 40% in the control group.

Endotherapy is not feasible in all patients (large hiatus hernia and obese), however can be considered in a selected group of patients with mild esophagitis, small hiatal hernia (<2 cm), endoscopic Hill’s grade II-III, and absence of Barrett’s esophagus. Similar to anti-reflux surgery, objective evidence of GERD should be documented and motility disorder should be ruled out in patients with GERD undergoing endotherapy.

43. The complications of GERD include peptic stricture, Barrett’s esophagus and GI bleeding.

GI bleeding in GERD is predominantly seen in patients with erosive esophagitis; the prevalence is as high as 8.2%. Factors associated with bleeding are severe esophagitis, low performance status and anticoagulant therapy. Treatment with PPI is the standard treatment option.

Barret’s esophagus (BE) is a premalignant condition in which the normal stratified squamous epithelium of the distal esophagus is replaced by columnar mucosa with intestinal specialized metaplasia. BE should be diagnosed when normal light pink color of esophagus is replaced by salmon pink color of gastric mucosa extending ≥1 cm above the gastrooesophageal junction. The Prague C and M classification system is commonly used for characterization BE on endoscopy. In Prague classification C stands for circumferential extension of metaplasia and M for maximal length of metaplasia (length between the most proximal point of columnar epithelium and the gastroesophageal junction). The risk factors for BE in the Asia-Pacific region are ethnicity, older age and male gender, long duration of reflux symptoms, abdominal obesity and smoking. Prevalence of BE in India ranges from 2.6% - 9% of patients with GERD.

Conclusion

The prevalence of GERD in large population-based studies is approximately 10% and is probably increasing due to lifestyle changes and increase in obesity. H. pylori infection has a negative association with GERD. Diagnosis of GERD should be mainly based on symptoms in the community, and empiric treatment with PPI/H2RA should be given. All PPIs in equipotent doses are similar in their efficacy in the management of symptoms. Patients with symptoms not adequately responding to PPI trial are regarded as having PPI-refractory GERD. Invasive investigations should be limited to patients with alarm symptoms and those with refractory GERD. The management algorithm is provided in Figure 1.


111. Gough AL, Long RG, Cooper BT, et al. Lansoprazole 40 mg once a day is equally effective as lansoprazole 30 mg twice a day in symptom control of patients with gastro-oesophageal reflux disease: a randomized double-blind, placebo-controlled dose-finding study. Aliment Pharmacol Ther 1999; 13:913–9.


