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ORIGINAL ARTICLE

Indian consensus on gastroesophageal reflux disease in adults: A position statement of the Indian Society of Gastroenterology

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Abstract

The Indian Society of Gastroenterology developed this evidence-based practice guideline for management of gastroesophageal reflux disease (GERD) in adults. A modified Delphi process was used to develop this consensus containing 58 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 10 on epidemiology, 8 on clinical presentation, 10 on investigations, 23 on treatment (including medical, endoscopic, and surgical modalities), and 7 on complications of GERD. When the proportion of those who voted either to accept completely or with minor reservation was 80% or higher, the statement was regarded as accepted. The prevalence of GERD in India ranges from 7.6% to 30%, being < 10% in most population studies, and higher in cohort studies. The dietary factors associated with GERD include use of spices and non-vegetarian food. *Helicobacter pylori* is thought to have a negative relation with GERD; *H. pylori* negative patients have higher grade of symptoms of GERD and esophagitis. Less than 10% of GERD patients in India have erosive esophagitis. In patients with occasional or mild symptoms, antacids and histamine H_2 receptor blockers (H2RAs) may be used, and proton pump inhibitors (PPI) should be used in patients with frequent or severe symptoms. Prokinetics have limited proven role in management of GERD.

Keywords Barrett's esophagus · Esophageal manometry · Esophageal pH monitoring · Proton pump inhibitors

Introduction

The prevalence of gastroesophageal reflux disease (GERD) was believed to be lower in Indian subjects; the prevalence in one study was 7.6% [1]. Other recent population based studies found a similar prevalence [2]. One population based study found a higher prevalence, almost comparable to that in the Western population [3]. Cross-sectional studies [4] show a higher prevalence of reflux symptoms. There are no population-based data on prevalence of Barrett's esophagus (BE) in patients with GERD in India; one study reported a frequency of 2.6% among GERD patients in a tertiary hospital in India [5].

The Indian Society of Gastroenterology (ISG) Task Force (TF) on GERD made a set of consensus statements for the diagnosis and management of GERD in India.

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Methods

A modified Delphi process [6] 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 ISG TF members. The first vote was conducted by SurveyMonkey, without explanation or justification for the statements [6]. Feedback regarding the statements was collated and modifications were 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 ISG TF members met in Mumbai and discussed the 82 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. Nineteen statements were deleted, five were combined into other statements; finally a total of 58 statements were modified and retained. An additional online voting round was conducted for approval of the modified statements. The participants were 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 TF on the Periodic Health Examination (Table 1) [7].

A total of 43 experts completed the online survey, and 34 attended the face-to-face meeting. The statements are listed in Table 2.

Epidemiology

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

Voting percentage: A 87.5, B 12.5
Level of evidence: III
Grade of recommendation: C

The definition of GERD varies among studies. A standard definition would facilitate comparison among studies and application of guidelines. The common symptoms of GERD are heartburn and sour regurgitation. The study by the ISG TF on epidemiology of GERD in India had used heartburn and/or regurgitation with symptom duration of at least once a week for at least a month as the definition of GERD [1]. We included "complications" in the definition to make it more comprehensive. The Montreal Global Consensus Definition of GERD also considered complications as a part of the definition [8]. GERD can also manifest with extraesophageal symptoms such as cough and laryngitis, but these symptoms occur even in the absence of GERD and were therefore not included in the definition.

Table 1 Grade of recommendation, level of evidence, and acceptance on voting

Quality of evidence		Strength of recommendation		Voting recommendation	
Grade	Description	Grade	Description	Option	Description
I	Evidence obtained from at least one randomized controlled trial	A	There is good evidence to support the statement	A	Accept completely
II-1	Evidence from well-controlled trials without randomization	B	There is fair evidence to support the statement	B	Accept with some reservation
II-2	Evidence from well-designed cohort or case–control study	C	There is poor evidence to support the statement	C	Accept with major reservation
II-3	Evidence from comparison between time or place with or without intervention	D	There is fair evidence to refute the statement	D	Reject with reservation
III	Opinion of experienced authorities and expert committees	E	There is good evidence to refute the statement	E	Reject completely

Table 2 List of statements of the Indian Society of Gastroenterology Task Force (ISG TF) consensus on gastroesophageal reflux disease (GERD)

No.	Statement
Epidemiology	
1.	GERD is defined as reflux of gastric content into esophagus, resulting in symptoms and/or complications.
2.	GERD is common in India, in both urban and rural populations.
3.	Obesity is a risk factor for GERD.
4.	Consumption of tobacco is a risk factor for GERD.
5.	Evidence of alcohol consumption as a risk factor for GERD is lacking.
6.	Dietary factors have been linked with GERD symptoms.
7.	There is inverse association between the prevalence of *Helicobacter pylori* infection and GERD.
8.	Patients with GERD may have additional symptoms of functional dyspepsia.
9.	Eosinophilic esophagitis should be looked for in patients with refractory GERD.
10.	GERD has an adverse impact on the quality of life.
Symptoms	
11.	The symptoms of GER are exacerbated with increase in intra-abdominal pressure.
12.	The symptoms of GER are related to posture.
13.	Symptoms of GERD lead to sleep disturbance.
14.	Refractory GERD is defined as nonresponse to optimal PPI therapy over 8 weeks.
15.	GERD should be considered in patients with difficult-to-treat nonseasonal asthma and chronic cough.
16.	Diagnosis of reflux laryngitis cannot be made by laryngoscopic findings alone.
17.	Noncardiac chest pain can be caused by GERD.
18.	The symptoms of GERD are aggravated by some dietary factors.
Diagnosis and investigations	
19.	Clinical diagnosis of GERD is usually based on symptoms and investigations should be used in a selected group of patients.
20.	(a) Patients with GERD and those with long-standing symptoms should undergo upper gastrointestinal endoscopy at least once in their lifetime. (b) Patients with GERD undergoing endoscopy should be evaluated for grades of esophagitis, hiatus hernia, and Barrett's esophagus. (c) The Los Angeles (LA) classification system should be used when describing the endoscopic appearance of erosive esophagitis. (d) Endoscopic description is sufficient without histology, for the diagnosis of erosive esophagitis.
21.	Symptoms do not necessarily correlate with endoscopic severity of GERD.
22.	24-h impedance pH monitoring off PPI is currently the gold standard for diagnosis of GERD.
23.	Bravo pH recorder has a limited role in the diagnosis of GERD in India.
24.	(a) Patients with inadequate symptom relief may benefit from pH metry and/or pH impedance study. (b) Mere presence of nocturnal acid breakthrough without esophageal acidification and associated symptom may not be clinically significant.
25.	(a) Esophageal manometry has no role in the diagnosis of GERD. (b) Patients undergoing 24-h pH metry should undergo esophageal manometry to localize the LES for placement of the pH probe.
26.	Tests for *Helicobacter pylori* are not routinely needed in patients with GERD.
27.	Barium esophagogram has a limited role in the diagnosis of patients with GERD.
28.	Emerging techniques, currently of experimental value, to investigate patients with GERD include narrow band imaging, endomicroscopy, and EndoFLIP.
Treatment	
Lifestyle modifications	
29.	Triggers for reflux symptoms (caffeine, smoking, alcohol, chocolates, spicy food) if identified should be avoided.
30.	Weight reduction is recommended for obese/overweight patients with GERD.
31.	Elevation of head end of bed is advisable for symptomatic supine refluxers.
32.	Patients of GERD should avoid lying down within 2 h after a meal.
Pharmacological therapy	
33.	For occasional GER symptoms, antacids and H2RAs can be used.
34.	PPIs are superior to H2RAs which are superior to placebo in the treatment of GERD.
35.	A standard dose PPI for 4 weeks should be the first line of therapy when used empirically or in patients with NERD.
36.	In patients with erosive esophagitis, daily PPI should be given for 8 weeks.

Table 2 (continued)

No.	Statement
37.	For recurrence of symptoms after initial treatment in patients with uninvestigated GERD or NERD, the lowest effective dose of PPI or H2RA should be advised.
38.	For maintenance therapy in severe erosive esophagitis, long-term PPI should be offered.
39.	In the presence of esophageal strictures, long-term daily PPI maintenance therapy should be given.
40.	In patients with nocturnal reflux symptoms, optimizing PPI therapy or adding an H2RA at night should be considered.
41.	If there is a partial response to once-daily PPI, increasing the dose of the same PPI to twice daily, or switching to another PPI at once-daily dose, may be considered.
42.	Prokinetics have no proven role in routine management of GERD.
43.	Nonresponders to 4 weeks of PPI therapy should be further evaluated.
44.	In suspected reflux chest pain syndrome, twice-daily PPI therapy as an empirical trial may be given for 4 weeks, after a cardiac etiology has been ruled out.
45.	PPIs can be considered in patients with nonseasonal asthma and chronic cough in the presence of typical reflux symptoms.
46.	All the available PPIs in equipotent doses have similar efficacy for symptom control.
47.	Injudicious use of long-term PPIs should be avoided.
Complications of GERD	
Barrett's esophagus	
48.	The description of BE on endoscopy should be done using the Prague C and M criteria.
49.	Columnar epithelium should extend for more than 1 cm above the proximal gastric fold to call it ESEM.
50.	Patients with esophageal biopsies showing columnar metaplasia is said to have BE.
51.	The presence of dysplasia should preferably be confirmed by an experienced pathologist.
52.	There is no study from India to support routine surveillance in patients with nondysplastic BE.
53.	BE should be excluded by repeat endoscopy, after 8 weeks of PPI treatment, in cases of severe erosive esophagitis (LA grades C and D).
Peptic stricture	
54.	Patients with peptic stricture should receive continuous PPI to reduce the need for repeat dilation.
Endoscopic management	
55.	Endoscopic antireflux procedures are evolving therapeutic modalities for a select group of patients with GERD.
Surgical management	
56.	Surgery for GERD is an effective alternative to long-term medical therapy and should be offered to appropriately selected patients.
57.	Patients referred for surgery should undergo preoperative evaluation for esophageal motility and confirmation of GERD.
58.	Surgery should be avoided in patients of GERD with gastroparesis.

GERD gastroesophageal reflux disease, *GER* gastroesophageal reflux, *PPI* proton pump inhibitors, *H2Ras* histamine H2 receptor blockers, *NERD* nonerosive reflux disease, *BE* Barrett's esophagus, *ESEM* endoscopically suspected esophageal metaplasia, *LES* lower esophageal sphincter. *EndoFLIP* endoscopic functional luminal imaging probe

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

Voting percentage: A 87, B 13
Level of evidence: II-2
Grade of recommendation: A

There are both community- and cohort studies on the prevalence of GERD in India. The multicenter study by the ISG TF was based on convenience sampling and included 3224 subjects [1]. Twelve centers across the country participated, and subjects from urban (11) and rural (2) areas and slums (2) were recruited. The overall prevalence of GERD was 7.6%: 6.7% in northern India and 8.4% in the southern parts. Two community-based studies were done in southern India (Vellore, Tamil Nadu; and Trivandrum, Kerala) and one in Ladakh, a high-altitude zone in northern India [2, 3, 4]. The study from Vellore [2] used a definition of GERD similar to that used by the ISG TF, while the other two used a questionnaire-based diagnosis. The study from Vellore [2] included 6174 subjects (3017 rural, 3157 urban) and reported a prevalence of GERD of 8.2%; the prevalence was higher in the urban area as compared to the rural area (11.1% vs. 5.1%). The study from Trivandrum had a smaller number (1072) of participants; the overall prevalence was 22.2%, being 29% among the 341 urban subjects and 19% among 741 rural subjects [3]. Among the 905 subjects from Ladakh [4], a high altitude area, 18.7% had GERD; the prevalence in the rural area (23%) was more than in the urban area (13.1%), unlike in the other two community-based studies. Sharma et al. [9] did a questionnaire-based study and reported that 653 (16.2%) of 4039 employees of the All India Institute of Medical Sciences, New Delhi had GERD; 3.6% had heartburn on a daily basis and 5.9% on a weekly basis. Another study in hospital employees looked at

the prevalence of heartburn as a categorical variable and reported that 28.5% of hospital employees gave history of heartburn [10].

It is therefore clear that GERD is not an uncommon problem, and occurs in almost 10% of both the rural and urban populations of India [11]. The global prevalence is estimated to be around 15%, with higher prevalence in North American and European nations [12, 13]. The prevalence in India is almost comparable to that in the West and is higher than in many Asian countries [11, 12, 13].

3. Obesity is a risk factor for GERD.

Voting percentage: A 88.5, B 11.5
Level of evidence: II-2
Grade of recommendation: A

Obesity may affect the gastroesophageal junction (GEJ) barrier function in multiple ways. These include raised intragastric pressure, increased number of transient lower esophageal sphincter (LES) relaxations, esophageal dysmotility, and reduction in pressure of the LES [14]. Obesity has been associated with both nonerosive and erosive GERD [15]. Data from the ISG TF showed a prevalence of 8.9% in individuals with BMI > 25 compared to 7.1% in those with body mass index (BMI) ≤ 25 ($p = 0.08$) [1]. The community-based studies from Vellore and Trivandrum and a study from Delhi in hospital employees showed 2 to 4 times higher risk of GERD with BMI > 25, which increased further when BMI was > 30 [2, 3, 9]. Globally, countries with higher prevalence of obesity have higher prevalence of GERD [14]. In India too, data from the National Nutrition Monitoring Bureau [16] has shown an increasing trend of obesity in both women and men in India. A meta-analysis of 20 studies showed odds ratio (OR) of 1.49 (1.43–1.55) for GERD in overweight subjects and 2.16 (2.05–2.28) in obese subjects [17].

4. Consumption of tobacco is a risk factor for GERD.

Voting percentage: A 66.6, B 22.2, C 11.1
Level of evidence: II-2
Grade of recommendation: C

Consumption of tobacco is mainly in the form of smoking or chewing. Tobacco may contribute to GERD by inhibiting LES pressure and an adverse effect on the esophageal epithelium [18]. The association between GERD and tobacco consumption has been inconsistent. In the study by the ISG TF, 16.7% of patients with GERD consumed tobacco compared to 14.3% without (p = ns) [1]. Similarly, the community-based studies from southern India and Ladakh showed no association between GERD and tobacco consumption [2, 3, 4]. A hospital-based study from Delhi found current smoking but not tobacco chewing as a risk factor for GERD [9]. In a systematic review, five of seven population-based studies showed positive association between tobacco consumption and smoking [18]. A recent meta-analysis, which included 30 studies, found higher prevalence of reflux symptoms in current smokers than nonsmokers (OR 1.26, 1.04–1.52) [13]; however, there was significant heterogeneity among the studies. The overall global evidence therefore suggests tobacco consumption as a risk factor for GERD; patients should, therefore, be advised against tobacco consumption in any form.

5. Evidence for alcohol consumption as a risk factor for GERD is lacking.

Voting percentage: A 79.2, B 16.6, C 4.1
Level of evidence: II-2
Grade of recommendation: A

Alcohol may affect esophageal motility and LES function, but available evidence does not support its role as a risk factor for GERD [18]. The ISG TF reported similar prevalence of alcohol consumption in patients with (16.4%) and without (15.2%) GERD [1]. The community-based study from Vellore had similar proportion of subjects taking alcohol in the GERD (9.1%) and no-GERD (9.4%; OR 1.0, 0.7–1.3) groups [2]. The prevalence of alcohol consumption was very high (> 70%) in the study from Ladakh, but this was similar in patients with and without GERD [4]. A recent meta-analysis included 24 studies with data on alcohol consumption and GERD [13]. GERD was present in 20.3% of alcohol consumers vs. 18.1% in the rest (OR 1.11, 0.85–1.46). Thus, current data do not support higher risk of GERD among those consuming alcohol.

6. Dietary factors have been linked to gastroesophageal reflux symptoms.

Voting percentage: A 69.2, B 23.1, C 7.7
Level of evidence: III
Grade of recommendation: C

The list of food items and drinks explored as risk factors for GERD is extensive [19]. Dietary modification is often recommended for managing GERD, although evidence for several recommendations is lacking [19]. Studying dietary factors is challenging due to the large number of variables involved, including amount, duration, and consistency of specific food items as well as regional variations. The community-based studies from Ladakh and Vellore, and data from the ISG TF showed non-vegetarian food as risk factor for GERD [1, 2, 4]. The ISG TF collected dietary information in great details, including data on fruits, spices, aerated drinks, tea/coffee, cereals, and meat/fish, but only non-vegetarian food showed a positive association on multivariate analysis [1]. Frequent meat consumption was associated with GERD (OR 1.8, 1.0–3.3), whereas milk intake had no significant impact in the study from Vellore [2]. Lack of meat in the diet had a protective role in the Ladakh study (OR 0.84, 0.71–0.99) [4]. non-vegetarianism showed no association with GERD in the cross-sectional study from Delhi (OR 0.93, 0.78–

1.11) [9]. In a small study of 358 medical students, Arivan and Deepanjali that reported that frequent consumption of aerated drinks (OR 3.63), and tea or coffee (OR 4.65) was associated with GER symptoms [20].

Patients with GERD are often advised to cut down on tea, coffee, and aerated drinks, although a meta-analysis of 15 studies showed no significant association between coffee intake with GERD (OR 1.06, 0.94–1.19) [21]. Thus, while data from India suggest that non-vegetarian food may trigger reflux symptoms, recommendations on other food items need to be individualized depending on response of symptoms to specific food items.

7. There is inverse association between the prevalence of *Helicobacter pylori* infection and GERD.

Voting percentage: A 50, B 42.3, C 7.7
Level of evidence: II-2
Grade of recommendation: A

H. pylori infection is common in India. The effect of *H. pylori* on gastric acid secretion may influence acid reflux [22]. Reports from Western countries have been conflicting, while studies from Asia have often shown an inverse association between *H. pylori* infection and GERD [23]. The prevalence of *H. pylori* infection in Asian countries appears to be on the decline, while the prevalence of GERD has been rising [23]. A study on 2580 adult patients from China showed a protective effect of *H. pylori* (OR 0.37, 0.14–0.98) on erosive esophagitis [24]. A large prospective study from Korea showed a prevalence of reflux esophagitis of 3.3% in patients with *H. pylori*-infected individuals compared to 6.4% in the noninfected group ($p < 0.001$) [25]. After eradication of *H. pylori* infection, the prevalence of reflux in the eradicated group increased to more than twice than in the group with persistent infection. Data from India on this subject are limited [22]. The negative trends noted from other Asian countries need confirmation in the Indian population.

8. Patients with GERD may have additional symptoms of functional dyspepsia.

Voting percentage: A 77.8, B 18.5, D 3.7
Level of evidence: II-2
Grade of recommendation: B

Functional gastrointestinal disorders (FGID) do not always occur as isolated entities; there is a significant overlap between these disorders. This is not surprising, considering their shared pathogenetic mechanisms, such as dysmotility and hypersensitivity [26]. The ISG TF study reported abdominal pain in 34.3%, difficulty in passing stool in 21.7%, and mucus in stool in 9% of patients with GERD, which were significantly higher than those without GERD [1]. A meta-analysis of 8 studies revealed GERD in 30.8% patients with dyspepsia [26]. The ISG TF multicenter study on IBS reported heartburn in 37.1% of 1301 patients with IBS [27]. A meta-analysis of close to 50,000 subjects reported GER symptoms in 42% (30% to 55%) of patients with IBS [28]. It is therefore important to assess for overlapping FGID in patients with GERD as the former may influence management and response to treatment.

9. Eosinophilic esophagitis (EoE) should be looked for in patients with refractory GERD.

Voting percentage: A 65.4, B 26.9, C 7.7
Level of evidence: III
Grade of recommendation: C

The typical symptom associated with EoE is dysphagia, but reflux symptoms may also occur [29, 30]. While EoE is more commonly reported from the West, it also occurs in the Asian population albeit at a lower frequency [29]. The reported prevalence of EoE among patients with GERD has varied from 0.3% to 7% in reports from Asia [29]. In a prospective study from Delhi, EoE was present in 3.2% of 185 patients with GERD [31]; nonresponse to PPI was one of the predictors. Therefore, it is important to consider this entity in refractory patients with GERD.

10. GERD has an adverse impact on quality of life.

Voting percentage: A 80, B 16, C 4
Level of evidence: II-2
Grade of recommendation: A

GERD has a negative impact on various activities such as sleep, dietary intake, and occupation and also affects emotional well-being [32]. Assessment of the health-related quality of life (HR-QoL) is important to understand the overall impact of disease on the patient and to monitor the effect of therapy [33]. Studies have used both generic instruments such as short form (SF)-36 and specific instruments such as GERQ and GORD-HRQoL to assess QoL in patients with GERD [33]. The use of different instruments makes comparison difficult. A systematic review included five studies in which physical aspects and three studies where mental aspects of QoL were assessed following therapy with PPI [34]. Responders to PPI fared better on both physical and mental aspects of QoL compared to nonresponders. Another review showed a higher adverse effect on QoL in women and in younger individuals with GERD [33]. The ISG TF on GERD is currently accumulating data on QoL as part of a multicenter study on GERD (unpublished data).

Clinical features

11. The symptoms of GER are exacerbated with increase in intra-abdominal pressure.

Voting percentage: A 68, B 28, E 4
Level of evidence: II-1
Grade of recommendation: B

Transient increase in intra-abdominal pressures leads to an adaptive and protective increase in LES pressure under physiological conditions. This protective mechanism may be deficient in patients with GERD with low LES pressures. Bitnar et al. [35] demonstrated that patients with resting LES pressure < 10 mmHg and upper esophageal sphincter (UES) pressure < 44 mmHg had significantly lower rise in the respective pressures in response to leg raising, as compared to patients with normal resting LES and UES pressures. Exercises or maneuvers that require bending can also lead to increase in intra-abdominal pressure. Sodhi et al. [36] demonstrated significantly higher esophageal acid exposure after forward-bending exercises, with median (range) reflux time percentage during the 30 min of exercise being 6.6 (0–60) compared with 0.0 (0–80) before exercise. This effect was more pronounced in patients who had a combination of both supine and upright reflux.

12. The symptoms of GER are related to posture.

Voting percentage: A 43.5, B 43.5, C 13
Level of evidence: I
Grade of recommendation: B

Supine position predisposes to reflux due to loss of effect of gravity. This allows the refluxed contents to move orad and remain in the esophagus longer. Khan et al. [37] found that elevating the head end of the bed with wooden blocks of 20 cm in patients with symptomatic nocturnal reflux resulted in significantly decreasing the mean (SD) supine reflux time from 15% (8.4) to 13.7% (7.2). The acid clearance time was significantly reduced from 3.8 (2) to 2 (1.6) min. Almost two-thirds of patients reported improvement in sleep disturbance. A prospective study using a position therapy device, that allowed participants to sleep in the left lateral recumbent posture and with head elevated by 15–20°, showed significant improvement in GERD Symptom Severity and Impact Questionnaire and GERD HR-QoL questionnaire scores over a period of 2 weeks [38]. Two other randomized trials also demonstrated the efficacy of head-end elevation with either a block under the head-end or a wedged bed [39, 40]. Right lateral position leads to higher esophageal acid exposure and more transient LES relaxations as compared to left lateral position in the postprandial period [41]. In another study, right lateral decubitus was associated with greater percent time pH < 4 and longer esophageal acid clearance as compared to the left, supine, and prone positions [42].

13. Symptoms of GERD leads to sleep disturbance.

Voting percentage: A 80, B 20
Level of evidence: II-2
Grade of recommendation: B

Nocturnal GERD is promoted by poor esophageal motility and delayed acid clearance from the esophagus at night [43]. GERD has been associated with sleep disturbance, including arousal from sleep and increased wakefulness [44, 45]. In the ISG TF study on GERD, 34.7% of subjects had nocturnal symptoms and 15% had elevated the head end of the bed. In a study from Kerala [3], 10.2% of subjects had nocturnal symptoms of GERD. A study from Chennai [46] among pregnant patients reported nocturnal symptoms in 54%. Similar studies from the USA [47] showed 73% of patients to have nocturnal symptoms. Nocturnal acid breakthrough, defined as persistent reduction of intragastric pH below 4 for more than 60 min during the night, occurs in 39% of patients with GERD while on PPI [48].

14. Refractory GERD is defined as nonresponse to optimal PPI therapy over 8 weeks.

Voting percentage: A 77, B 18, C 5
Level of evidence: III
Grade of recommendation: C

There is no universal definition of refractory GERD. A recent Asian Pacific Association of Gastroenterology (APAGE) steering committee defined refractory GERD as persistent and troublesome GERD symptoms unresponsive to at least 8 weeks of a standard dose of PPI [29]. The American Gastroenterological Association (AGA) observes that while there is no established consensus regarding the definition of refractory GERD in terms of symptom burden, the degree of therapeutic response, and PPI dose at which failure occurs, is largely a patient-driven phenomenon [49].

Optimal PPI therapy refers to standard dose PPI twice a day (e.g. pantoprazole 40 mg given twice a day). There are no data from India on the profile of GERD refractory to PPI. A study from China showed that the prevalence of PPI-refractory GERD symptoms was 37.9% in those with non-erosive reflux disease (NERD) after a standard dose of PPI for 6 months [50]. In a Korean study, refractory GERD symptoms occurred in 16.7% of patients with NERD and 6.6% of those with erosive esophagitis after 8 weeks of PPI treatment [51]. A post hoc analysis of four randomized controlled trials (RTC) showed that between 14% and 19% of patients with GERD partially responded to PPI therapy; nonresponse to PPI was rare (NERD 2.4%, erosive esophagitis 1.4%) [52]. The differences in the reported prevalence of refractory GERD are likely due to different definitions, patient selection, and variations in the dosage of PPI.

15. GERD should be considered in patients with difficult-to-treat non-seasonal asthma and chronic cough.

Voting percentage: A 82, B 18

Level of evidence: II-2
Grade of recommendation: B

GERD can precipitate asthma or cough by vagally mediated esophagotracheobronchial reflex [53, 54], bronchial hyperreactivity [54], and microaspiration of gastric contents [55, 54]. Contrarily, asthma is known to promote reflux by increasing the pressure gradient between the abdomen and the thorax from the increased work of breathing and lung hyperinflation, and thereby results in herniation of the LES into the thoracic cavity [56].

The prevalence of GERD in patients with difficult-to-treat asthma (defined as poor asthma control despite being on optimal medication and requiring frequent rescue β2-agonist inhaler therapy) was found to be 70% by esophageal pH monitoring [57]. Almost one-fourth of these patients had no reflux symptoms. On treatment with omeprazole, significant improvement was observed in pulmonary function parameters. In a study from Chennai [58], typical GERD symptoms were present in 51% of asthmatics. In another study, symptomatic or endoscopic GERD was found in 58% of asthmatics as compared to 32.8% of patients with rhinitis and urticaria ($p < 0.02$) [59]. Of all asthmatics having GERD, 69% had mild asthma, 27.5% had moderate, and 3.4% had severe disease; 10% of asthmatics with GERD had no reflux symptoms.

GERD is reported as a cause of chronic cough in as many as 40% of patients [60, 61]. In the ISG TF, 15.5% of patients with GERD had nocturnal cough [1]. In up to 75% of cases, GERD-related cough may present with no GI symptoms [61]. Using impedance/pH manometry in patients with chronic cough, Smith et al. [62] demonstrated that 48% of patients had positive symptom association probability for cough preceded by reflux, 56% positive symptom association probability for reflux preceded by cough, and 32% had both. Thus, the relationship between cough and GERD is bilateral.

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 [63]. Acid-suppressive therapy in the treatment of undiagnosed chronic cough is not effective [64]. A significant number of patients do not report improvement despite aggressive acid-suppressive therapy. Evidence for the efficacy of PPI in treating cough is scant, but it may be efficacious in patients with objective evidence of GERD (endoscopy or physiological monitoring).

16. Diagnosis of reflux laryngitis cannot be made by laryngoscopic findings alone.

Voting percentage: A 91, B 9
Level of evidence: II-2
Grade of recommendation: B

Laryngopharyngeal reflux (LPR) is defined as retrograde flow of stomach contents into the larynx and pharynx whereby this material comes in contact with the upper aerodigestive tract [65]. Manifestations of LPR include a wide range of laryngeal and pharyngeal symptoms such as change in voice, burning sensation in the substernal/epigastric region, regurgitation, dysphagia, throat pain, cough, foreign-body sensation in the throat, and frequent throat clearing [66].

The most common laryngoscopic findings include subglottic edema, ventricular obliteration, erythema or hyperemia, vocal fold edema, generalized laryngeal edema, posterior commissure hypertrophy, granuloma or granulation tissue, and excess mucus in the larynx [67]. However, these findings are subjective in nature and are found in up to 86% of healthy controls [68].

The role of 24-h pH monitoring in the diagnosis of LPR has been questioned due to low sensitivity, and there is no consensus on the correct site of placement of the pH probe and interpretation of the results [69]. In a study by Maldhure et al. [66], there was poor correlation between the reflux finding score (calculated from findings obtained by flexible nasopharyngolaryngoscopy), Koufman Reflux Symptom Index, and DeMeester score from dual-probe pH recording. The lack of agreement between these tests may be because of the fact that these evaluate different features of the disease. No single test is diagnostic, and hence, it advisable to use a combination of tests to diagnose LPR such as laryngoscopy, upper GI endoscopy and 24-h esophageal pH studies.

17. Non-cardiac chest pain can be caused by GERD.

Voting percentage: A 70, B 26, C 4
Level of evidence: II-3
Grade of recommendation: C

Non-cardiac chest pain (NCCP) is defined as recurring angina-like or substernal chest pain believed to be unrelated to the heart disease after reasonable cardiac evaluation [70]. GERD is implicated in up to 60% of patients with NCCP [71]. A high prevalence of GERD in patients with NCCP has also been noted in Indian studies [72]. In the ISG TF report, 22.4% of subjects with GERD had chest pain as compared to 4% of non-GERD subjects; of these, 31% had pain more than once per week [1].

A diagnostic approach to NCCP has been proposed for resource-constrained settings. Initial evaluation is suggested with upper GI endoscopy, with further testing (esophageal manometry, pH recording) only in those with normal endoscopy [72]. Symptomatic improvement with PPI is seen in most patients. In a study by Jain, 85% of patients had relief in symptoms with a 2-week course of PPI therapy [72].

18. The symptoms of GERD are aggravated by some dietary factors.

Voting percentage: A 68, B 28, C 4
Level of evidence: II-2

Grade of recommendation: C

Dietary factors aggravate pre-existing GERD. In a recent review, food items like chocolate, spicy foods, citrus foods, caffeine, carbonated beverages, fatty foods, and mint worsened symptoms of GERD [73]. A high-fat diet produced higher esophageal acid exposure in patients with reflux esophagitis and NERD as compared to healthy controls [74]. A high-carbohydrate diet has been demonstrated to produce higher number and duration of acid reflux episodes in patients with GERD [75]. In a study by Shapiro et al. [76], increased consumption of cholesterol, saturated fatty acids, and percentage calories from fat enhanced the perception of an acid reflux event.

The establishment of causation of symptoms with dietary factors is difficult due to the heterogeneity and scarcity of data and variety of confounding factors.

Investigations

19. The clinical diagnosis of GERD is usually based on symptoms, and investigations should be used in a selected group of patients.

Voting percentage: A 73, B 19, D 5.4, E 2.7
Level of evidence: I
Grade of recommendation: A

The cardinal symptoms of GERD are heartburn and sour regurgitation. Symptom-based diagnosis of GERD is only moderately accurate with reported sensitivity and specificity of 62% and 67%, respectively [77]. Improvement in symptoms on a PPI trial has reasonable sensitivity and specificity to diagnose GERD [77–79]. Specialized investigations to diagnose GERD, such as 24-h impedance pH metry, are neither widely available nor cost-effective in unselected patients, and their routine use is not warranted. However, investigations to confirm the diagnosis of acid reflux in patients with normal endoscopy (NERD), and to exclude other causes of heartburn such as functional heartburn and esophageal hypersensitivity, are indicated in a subset of patients.

20. a. Patients with GERD, and those with long-standing symptoms, should undergo upper GI endoscopy at least once in their lifetime.

Voting percentage: A 73.1, B 23.1, C 3.8
Level of evidence: I
Grade of recommendation: A

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

Voting percentage: A 92, B 8
Level of evidence: I
Grade of recommendation: A

c. The Los Angeles (LA) classification system should be used when describing the endoscopic appearance of erosive esophagitis.

Voting percentage: A 86.8, B 13.1
Level of evidence: III
Grade of recommendation: A

d. Endoscopic description is sufficient without histology, for the diagnosis of erosive esophagitis.

Voting percentage: A 68.4, B 29, D 2.6
Level of evidence: I
Grade of recommendation: A

Upper GI endoscopy should be done to determine whether the patient has erosive esophagitis and to grade esophagitis, to look for the presence of hiatus hernia and its type and size, and complications such as peptic stricture, BE, and its extent. The LA classification system [80, 81] should be used to describe the endoscopic appearance of erosive esophagitis. Early upper GI endoscopy is warranted in patients with alarm symptoms like dysphagia, recent onset symptoms, weight loss, GI bleed, age > 55 years, and family history of upper GI malignancy. In patients with no alarm symptoms, endoscopy may be done if there is no response to PPI. Endoscopic esophageal biopsy should be done if EoE is suspected, as this may present with heartburn.

Grade of esophagitis has important bearing on treatment, patient response, complications, and prognosis. Grades C and D esophagitis are infrequent in Indian patients with GERD [82, 83]. Dutta et al. [83] found that out of 566 patients, only 8.8% had erosive esophagitis and only 1.2% had grade C and D esophagitis. Higher grades of esophagitis are more often associated with manometric abnormalities such as reduced LES pressure and abnormal body motility [84], complications such as peptic stricture, and poorer QoL. Such patients may need lifelong PPI treatment, often at higher doses, and consideration for surgical intervention.

Hiatus hernia is often associated with GERD, and the larger its size, the greater the volume of reflux and re-reflux, with formation of an acid pocket [85]. Surgical correction may be needed for large hiatus hernia.

Esophageal biopsy is not routinely needed in patients with GERD. Histological features include thickening of basal layer and elongation of rete pegs and infiltration with inflammatory cells including eosinophils [86]. However, the number of eosinophils is less in patients with GERD than those with EoE (≥ 15/high power field).

There are scanty data on prevalence of BE (specialized columnar epithelium) in patients with GERD in India [87]. The endoscopic prevalence of BE has been reported in 9% of patients with GERD [88].

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

Voting percentage: A 96, B 4
Level of evidence: II-2
Grade of recommendation: A

There is poor relationship between the endoscopic severity of GERD and symptoms [48]. In fact, patients with endoscopy-negative GERD often complain of significant heartburn as esophageal hypersensitivity is a major determinant of symptoms [89]. For this reason, in the Rome IV algorithm, a new subgroup of patients with reflux hypersensitivity has been recognized and the role of visceral neuromodulators in its treatment has been highlighted. Elderly patients complain of less symptoms despite severe degree of endoscopic esophagitis. Patients with BE also may not have severe symptoms in the absence of significant esophagitis [90].

22. 24-h impedance pH monitoring off PPI is currently the gold standard for diagnosis of GERD.

Voting percentage: A 76.3, B 21, C 2.6
Level of evidence: III
Grade of recommendation: B

Reflux monitoring demonstrates evidence of excessive esophageal acid exposure time (AET) and an abnormal number of reflux events (events when pH decreases to <4). Hence, reflux monitoring is useful to confirm or exclude pathological GERD [91]. The addition of impedance to 24-h pH metry helps in detecting GERD even if the refluxate is neutral or alkaline, especially when the patient is on PPI [92]. Additionally, pH impedance allows measurement of association between symptoms and acid or nonacid reflux events. Commonly used indices like symptom index (SI) and symptom association probability (SAP) are useful to differentiate reflux hypersensitivity from functional heartburn [92]. In patients with endoscopy-negative GERD, 24-h impedance pH monitoring is the gold standard for diagnosis of GERD [92], as investigations such as upper GI endoscopy are insensitive. Ambulatory reflux monitoring is also indicated in patients with atypical symptoms, in PPI refractory patients, and prior to surgical treatment of GERD.

An AET of < 4% can be considered definitively normal (physiological) and > 6% can be considered definitively abnormal [91]. A total of > 80 reflux episodes per 24 h is considered as definitively abnormal, while a number < 40 is physiological [91].

Testing is performed off PPI in patients with unproven GERD (none, or LA grade A and B esophagitis), prior to surgery and atypical presentations. On PPI, testing is done in patients with proven GERD (LA grade C and D esophagitis, BE > 1 cm, or prior abnormal pH study) to establish causation of the refractory symptoms and to rule out ongoing reflux (acid or nonacid) despite PPI therapy [91, 92].

In an Indian study, six diagnostic tests were compared for accuracy to detect GERD. These were omeprazole challenge test, endoscopy, esophageal histology, barium swallow, scintigraphy, and 24-h pH monitoring [93]. pH monitoring had the highest diagnostic accuracy (82.2%) among all the tests [93].

23. Bravo pH recorder has a limited role in the diagnosis of GERD in India.

Voting percentage: A 51.3, B 46, C 2.7
Level of evidence: I
Grade of recommendation: B

The catheter-free Bravo esophageal pH capsule recorder, when implanted in the esophageal mucosa, sends data to an external receiver via radiofrequency telemetry. Studies have shown Bravo to be superior to catheter-based systems as it can record reflux for up to 96 h vs. 24 h for the latter [94]. Longer (96 h vs. 24 h) pH monitoring is helpful as there is physiologically high day-to-day variability in acid exposure. Patients reported higher nose pain, runny nose, throat pain, throat discomfort, and headache with the traditional pH monitoring but reported a higher chest discomfort with the wireless pH monitoring [95]. The single-use capsule is very expensive. It also cannot study impedance.

24. a. Patients with inadequate symptom relief may benefit from pH metry and/or pH impedance study.

Voting percentage: A 79, B 18.4, D 2.6
Level of evidence: III
Grade of recommendation: A

b. Mere presence of nocturnal acid breakthrough (NAB) without esophageal acidification and associated symptoms may not be clinically significant.

Voting percentage: A 39.4, B 52.6, C 5.2, D 2.6
Level of evidence: II-3
Grade of recommendation: C

Nonresponse to PPI may result from poor compliance, improper timing of administration (30–60 min before breakfast), inadequate acid suppression, neutral or alkaline volume reflux, NAB, or incorrect diagnosis. A 24-h pH/impedance monitoring while on PPI treatment

can detect inadequate acid suppression, volume reflux, and NAB.

NAB is defined as persistent reduction of intragastric pH below 4 for more than 60 min during the night, and nocturnal esophageal acidification is defined as a drop in esophageal pH of less than 4 for any duration during the night time. The detection of NAB requires a dual pH probe with distal channel placed in the stomach. NAB may not always be clinically significant. A few studies including two from India have shown that in spite of NAB, esophageal acidification and symptoms did not occur in patients with GERD during 24-h pH monitoring [48, 96, 97].

25. a. Esophageal manometry has no role in the diagnosis of GERD.

Voting percentage: A 23.6, B 57.8, D 18.4
Level of evidence: II-2
Grade of recommendation: A

b. Patients undergoing 24-h pH metry should undergo esophageal manometry to localize the LES for placement of the pH probe.

Voting percentage: A 56.7, B 27, C 8.1, D 8.1
Level of evidence: II-2
Grade of recommendation: A

During swallowing or neck movement, the LES moves orad by 2-3 cms. To avoid displacement of the pH probe due to this orad movement, the pH probe is placed 5 cm above the manomatrically defined LES [92]. The best way to determine the upper margin of LES is esophageal manometry. The GEJ may also be localized while pulling the pH probe across the LES and visualizing the acid drift, or during upper GI endoscopy, but these methods are inferior to manometry.

Esophageal manometry does not help to diagnose GERD. However, there are a number of anatomic and physiologic parameters including esophagogastric junction morphology, transient LES relaxation (TLESR), baseline esophageal body motor function, and contraction reserve, which help in the understanding of the disease process. Esophageal manometry may be normal in patients with GERD or may show low LES pressure and/or ineffective esophageal motility [84, 98, 99]. Patients with severe esophagitis are more likely to have manometric abnormalities. However, these findings are nonspecific and can occur even in the absence of GERD. A very low baseline LES pressure has prognostic importance as these patients may require larger dose of PPI, and lifelong treatment and may continue to have neutral volume reflux even after adequate acid suppression. Esophageal manometry also helps to diagnose major motor disorders such as achalasia, in which patients may report heartburn in about 30% of the time [100].

26. Tests for *Helicobacter pylori* are not routinely needed in patients with GERD.

Voting percentage: A 35.1, B 45.9, C 5.4, D 8.1, E 5.4
Level of evidence: II-2
Grade of recommendation: B

Helicobacter pylori has a negative relation with GERD. Patients with GERD and *H. pylori* infection have less acid exposure in the esophagus and less severe GERD. Chourasia et al. [101] found higher erosive esophagitis, lower esophageal pH, and longer reflux in patients without *H. pylori* infection. The patients with *H. pylori* had a lower serum pepsinogen-I to serum pepsinogen-II ratio suggesting a less acidic stomach. In another Indian study [102], *H. pylori*-negative patients had higher symptom scores and required higher doses of acid suppression and higher prevalence of esophagitis as compared to *H. pylori*-positive patients. Hence, for management of GERD, there is no role for testing for *H. pylori* or its eradication.

27. Barium esophagogram has a limited role in the diagnosis of patients with GERD.

Voting percentage: A 86.5, B 10.8, D 2.7
Level of evidence: II-2
Grade of recommendation: A

Barium swallow can detect spontaneous gastroesophageal reflux or it can be provoked by maneuvers. It may also detect esophageal strictures and hiatus hernia. However, barium swallow has a low sensitivity (67%) and specificity (47%) to identify GERD [103]. Additionally, barium tests cannot properly identify patients with increased acid exposure or positive reflux symptom association. Hence, barium studies are not of value in the diagnosis of GERD [86].

28. Emerging techniques, currently of experimental value, to investigate patients with GERD include narrow band imaging, endomicroscopy, and EndoFLIP.

Voting percentage: A 81, B 19
Level of evidence: I
Grade of recommendation: A

Narrow band imaging (NBI) uses spectral narrow band filter, which increases the contrast and allows for detection of changes in the microvasculature of the mucosa and to detect changes such as villous mucosal surface, mucosal islands, and microerosions in patients with GERD. Similar to NBI [86], other image enhancement techniques like iScan [104] and flexible spectral imaging color enhancement (FICE) [105] have been found to be useful in detecting minimal change

esophagitis in patients with NERD. NBI increases the sensitivity of white light endoscopy to detect GERD [86, 106, 107].

Confocal laser endomicroscopy (CLE) allows real-time in vivo histologic analysis of esophageal mucosa and identifies microalterations in the esophageal mucosa such as increased intrapapillary capillary loops and dilatation of intercellular space. CLE is helpful in diagnosing GERD in symptomatic patients with normal endoscopy [108]. EndoFLIP (endoscopic functional luminal imaging probe) assesses the distensibility of the EGJ. Patients with GERD have higher EGJ distensibility that may predict nonsurgical treatment outcomes [109]. Distensibility index at the EGJ overlaps considerably between normal healthy volunteers and GERD patients [110]. EndoFLIP may have value in understanding GERD pathophysiology, but more research is needed. Moreover, these newer techniques have not been validated in clinical settings, and hence, more data are necessary to assess the clinical utility of these techniques, particularly in the Indian setting.

Treatment

29. Triggers for reflux symptoms (caffeine, smoking, alcohol, chocolates, spicy food) if identified should be avoided.

Voting percentage: A 60, B 40
Level of evidence: III
Grade of recommendation: C

Lifestyle modification for GERD including dietary modification is based upon evidence and presumptions that certain food items and habits may trigger reflux by altering the antireflux mechanisms [73]. However, the evidence regarding food items is weak, inconsistent, and controversial, and hence, a general recommendation on avoidance of specific food items cannot be made. The relationship between coffee, caffeine, and GERD remains heterogeneous and unclear, with some studies reporting a positive and some reporting a nil or negative association. In an earlier study, intraesophageal infusion of coffee was shown to cause heartburn [111], while another study showed no changes in LES pressure with coffee in healthy individuals and in patients with GERD [112]. However, two large epidemiologic studies did not report any association between coffee and GERD [113, 114]. Cohen and Booth [115] showed an increase in LES pressure, while others showed no effect of coffee on LES pressure, total reflux time, and the number of reflux episodes [112].

The relationship between tobacco and GERD is also heterogeneous. Tobacco smoking has been reported to prolong acid clearance and decrease LES pressure [116]. Epidemiologically, questionnaire-based and case–control studies have reported higher rates of reflux symptoms in smokers and positive correlation between reflux symptoms and duration of smoking [117, 118]. However, studies on smoking cessation have been inconsistent, with earlier case–control studies showing no improvement in esophageal acid exposure or symptoms with smoking cessation [119–121] and a recent population-based cohort study of 29,610 participants reporting decreased reflux symptoms with smoking cessation in normal weight individuals [122].

Alcohol consumption has been associated with increased acid secretion, reduced LES pressure, increased TLESR, decreased gastric and esophageal emptying, and increased prevalence of reflux symptoms in drinkers; however, evidence for improvement in reflux symptoms and esophageal pH on alcohol cessation is lacking [113, 114, 123, 124].

There is weak evidence regarding the association between specific food items like chocolate, citrus fruits, carbonated beverages, spicy foods, fatty foods, mint, etc. and GERD symptoms. However, there are scanty data showing the effect of their cessation on symptom response [73]. Therefore, a general recommendation on cessation of any particular food item cannot be made, and it should be individualized with respect to patients' triggers.

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

Voting percentage: A 95.8, B 4.2
Level of evidence: I
Grade of recommendation: A

Obesity is one of the most important risk factors for GERD, and there is good evidence to show that weight loss is associated with reduction in symptoms of GERD. Two large population-based studies and two uncontrolled prospective studies showed that weight loss is associated with regression of GER symptoms [125]. In the Nurses' Health study, an observational cohort study of 10,545 women [126], and in the Nord-Trøndelag health study, a prospective population-based cohort study of 29,610 participants [127], there was a dose-dependent decline in reflux symptoms among those who had reduction in BMI, as compared to those without. Another study reported a significant improvement in esophageal pH and reflux symptom score after weight loss in eight extremely obese individuals [128]. In the other study of 34 patients with a mean BMI of 23.5, weight loss was associated with clinical as well as endoscopic improvement [129]. Similarly, three RCTs in severely obese individuals compared weight loss with gastric balloon vs. sham treatment and dietary guidance and showed that weight loss in both arms was associated with symptom improvement and improvement in esophageal pH [130–132]. In a RCT of over 300 patients, structured weight loss program was associated with improvement in reflux symptoms [133]. Bariatric surgery has also been associated with improvement in symptoms and pH metry and reduction grades of esophagitis [134].

31. Elevation of head end of bed is advisable for symptomatic supine refluxers.

Voting percentage: A 85, B 10, C 5
Level of evidence: I
Grade of recommendation: B

Elevation of the head end of the bed should decrease the reflux of acidic gastric contents in the esophagus, as shown by Stanciu and Bennett in 63 patients with GERD [135]. As compared to patients who slept flat, those with elevated head end of the bed had fewer and shorter reflux episodes and lesser reflux symptoms [135]. In another crossover RCT of 15 patients, elevation of head end of the bed on a 10-in. wedge was associated with significantly less acid reflux time that esophageal pH was less than 4 [39]. In a study from northern India, head end of the bed elevation with a 20-cm block for one week reduced esophageal acid exposure and acid clearance time in nocturnal refluxers and led to some improvement in heartburn and sleep [37]. However, in another RCT, there was no improvement with head end of the bed elevation in terms of symptom control [40].

32. Patients of GERD should avoid lying down within 2 h after a meal.

Voting percentage: A 75, B 25
Level of evidence: I
Grade of recommendation: C

In a crossover RCT of 30 patients with GERD, early meal (6 h before bedtime) was associated with less supine reflux as compared to late meal (2 h before bedtime) [136]. However, other studies in healthy individuals did not reveal such an association, with either no difference between late and evening meals [137], or effect of late meal on intragastric pH and observed only from midnight till 7 A.M. [138]. In the other study on 20 patients with GERD, esophageal pH symptoms were better when the same patients took a meal before 7 P.M. on one night than when they took a late evening meal on other night [139].

33. For occasional GER symptoms, antacids and H2RAs can be used.

Voting percentage: A 90.5, B 9.5
Level of evidence: I
Grade of recommendation: A

Histamine H_2 receptor blockers (H2RAs) reduce acid secretion by competitively antagonizing the H_2-receptors on the parietal cells. Antacids (basic aluminum, 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 (aluminum hydroxide and sucrose sulfate) 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 alginate/antacid combination (4 trials, 284 patients) in patients with GERD, all OTC medications were more effective than placebo in providing symptom relief [140]. In the H2RA trials, there was an absolute increase of 10% to 12% and relative increase of 19% to 41% over placebo in providing symptomatic relief. For antacids, the relative increase over placebo was 60% with antacid/alginate combination and 11% with antacids only. In a recent position paper by the Romanian Society of Neurogastroenterology, antacids were recommended for symptomatic relief in patients with mild GERD [141]. Antacids have the advantage of providing rapid symptom relief and have been found comparable to H2RAs [142]. Similarly, sucralfate has also been found to be superior to placebo and similar to H2RAs in providing symptomatic relief [143].

34. Proton pump inhibitors (PPIs) are superior to H2RAs, which are superior to placebo in the treatment of GERD.

Voting percentage: A 92, B 4, C 4
Level of evidence: 1
Grade of recommendation: A

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 [144]. PPIs should be administered 30–45 min before a meal for optimal effects. In a Cochrane review on short-term treatment of uninvestigated 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], H2RAs-OR 0.77 [2 trials, 95% CI 0.60 to 0.99]) and NERD group (PPIs-OR 0.71 [10 trials, 95% CI 0.65 to 0.78], H2RAs-OR 0.84 [2 trials, 95% CI 0.74 to 0.95]) [145]. PPIs were also more effective than H2RAs for heartburn remission, both in the empirical treatment group (OR 0.66 [7 trials, 95% CI 0.60 to 0.73]) and NERD group (OR 0.78 [3 trials, 95% CI 0.62 to 0.97)]). Overall, heartburn remission rates with PPIs vary from 37% to 61% in patients with NERD (placebo response 12.6%) or uninvestigated heartburn (placebo response 25.1%) and 56% to 77% (placebo response 7.5%) in patients with esophagitis, while healing of esophagitis occurs in 72% to 83% patients with erosive reflux disease (ERD) (placebo response 28.3%). However, improvement in regurgitation occurs only in 26% to 64% patients (placebo response 46.4%). The heartburn resolution with H2RAs occurs only in 48% to 56% patients (placebo response 22% to 40.6%), while only 41% patients with

ERD have healing of esophagitis (placebo response 20.3%) [146].

In a recent systematic review, none of the clinical trials had regurgitation as primary endpoint, and in the seven placebo-controlled trials on PPI, the therapeutic gain with PPI over placebo was ~17%, and this was >20% less than the improvement observed for heartburn [147].

The trials showing the efficacy of PPIs and H2RAs for treatment of GERD are summarized in Table 3.

35. A standard dose PPI for 4 weeks should be the first line of therapy when used empirically or in patients with NERD.

Voting percentage: A 86.4, B 9.1, C 4.5
Level of evidence: I
Grade of recommendation: A

The standard dose of all PPIs has been mentioned in Table 4. Patients with typical symptoms of GERD can be treated empirically with PPIs. However, in a meta-analysis of 15 studies, the pooled sensitivity and specificity of PPI trial vs. 24-h pH metry were 0.78 (95% CI 0.66–0.86) and 0.54 (95% CI 0.44–0.65), respectively, which were considered lower than the reference standards [148]. However, in the absence of alarm symptoms such as dysphagia, odynophagia, GI bleed, anorexia, and weight loss, PPI trial can be considered before any invasive diagnostic test. Further testing is indicated in patients not responding to 4 weeks of PPI therapy. Overall response rates on PPI in patients with uninvestigated heartburn reach up to 70% against the placebo response rate of 25% [146]. In the Cochrane review, PPIs were more effective than placebo and H2RAs when used empirically for heartburn relief [145]. Weijenborg et al. in their meta-analysis of 59 RCTs (26,885 patients) compared the symptom relief on PPIs in different groups of patients: heartburn without any testing, heartburn with normal endoscopy, heartburn with normal endoscopy and positive pH metry, and ERD [149]. The pooled response rate at 4 weeks in the four subgroups was (0.72 [95% CI 0.69–0.74]), (0.50 [95% CI 0.43–0.57]), (0.49 [95% CI 0.44–0.55]), and (0.73 [95% CI 0.69–0.77]) respectively, indicating the PPI response rates in patients with uninvestigated heartburn are lower than that in patients with ERD or confirmed NERD. The response rates at 8 weeks in patients with ERD (0.73 [95% CI 0.59–0.84]) and those with heartburn without any testing (0.47 [95% CI 0.43–0.51]) were similar to those at 4 weeks, indicating that PPI use beyond 4 weeks does not increase the response rates [150]. In the other meta-analysis of 17 studies (6072 patients with NERD), there was no difference in the pooled response rates between short (0.51 [95% CI 0.43–0.59]) and long duration (0.51 [95% CI 0.43–0.51]), as well as between low-dose (0.56 [95% CI 0.39–0.72]) and high-dose PPI therapy (0.48 [95% CI 0.40–0.56]) [151]. There is no difference between once- vs. twice-daily PPI in terms of symptom resolution at week 4 [152].

36. In patients with erosive esophagitis, daily PPI should be given for 8 weeks.

Voting percentage: A 87.5, B 12.5
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 (grades II–IV) erosive esophagitis [153]. Overall healing proportion with PPIs was 83.6% (95% CI 79–88%), with the rate of healing slowing down by 8 weeks (31.7%/week at 2, 17%/week at 4, and 10.6%/week by 8 weeks). Most trials evaluated healing rates on PPIs for 8 weeks, with only two trials extending PPI beyond 8 weeks, showing a minor increment from 86% to 91%. Symptom resolution in patients with erosive esophagitis ranges from 56% to 76%, and healing rate from 80% to 85% at 8 weeks [154]. The overall healing rates at 8 weeks (73% to 90%) were higher than those at 4 weeks (63% to 78%), with the difference becoming more obvious in patients with moderate to severe esophagitis at baseline (49% to 64% vs. 74% to 85%). The healing rates between 20 mg one daily and 10 twice-daily rabeprazole and 20 mg once-daily omeprazole were similar at 8 weeks in one trial [155]. However, in the other trial, the difference between twice-daily and once-daily doses at 8 weeks was more significant in patients with grade III or IV esophagitis [156]. Therefore, PPIs should be administered for 8 weeks in patients with erosive esophagitis, and twice-daily doses can be considered in patients with severe esophagitis at

Table 3 Summary of trials showing efficacy of proton pump inhibitors (PPI) and histamine receptor 2 (H2RA) antagonists for treatment of gastroesophageal reflux disease

Comparison	Empiric treatment group		NERD group	
	Number of trials	Odds ratio (95% CI)	Number of trials	Odds ratio (95% CI)
PPI vs. placebo	2	0.37 (0.32 to 0.44)	10	0.71 (0.65 to 0.78)
H2RA vs. placebo	2	0.77 (0.60 to 0.99)	2	0.84 (0.74 to 0.95)
PPI vs. H2RA	7	0.66 (0.60 to 0.73)	3	0.78 (0.62 to 0.97)

PPI proton pump inhibitors, *H2RA* histamine receptor antagonists, *NERD* nonerosive reflux disease

Table 4 Proton pump inhibitors that are available in India along with their standard dose

Drug name	Standard dose (mg OD)
Omeprazole	20
Lansoprazole	30
Pantoprazole	40
Esomeprazole	40
Rabeprazole	20
Ilaprazole	10
Dexlansoprazole*	30

OD once a day

* Dexlansoprazole can be taken independent of meal times; all other PPIs should be taken 30–60 min before meals

baseline. For maintenance therapy in severe erosive esophagitis, long-term PPI should be offered and this is discussed in detail in statement no. 38.

37. For recurrence of symptoms after initial treatment in patients with uninvestigated GERD or NERD, the lowest effective dose of PPI or H2RA should be advised.

Voting percentage: A 81, B 19
Level of evidence: I
Grade of recommendation: A

In one of the earlier studies, 117 patients with GERD were followed up for a median duration of 41 months [157]. Only 13 of these 117 patients were asymptomatic off therapy, rest either continued treatment on demand or the regularly, or had relapse of symptoms after stopping treatment. Inadomi et al. withdrew PPI in 73 patients (71 completed follow up) with uninvestigated GERD after they improved with PPI [158]; 41 (58%) remained asymptomatic over 1 year of follow up, and of these, 11 were off any medication, and 24 and 5 patients remained asymptomatic on H2RAs or antacids, respectively. A placebo-controlled trial randomized 424 patients with NERD to either 10 or 20 mg doses of on-demand omeprazole or to placebo [159]. Over 6-month follow up, remission rates were highest in the 20-mg group (83%), followed by the 10-mg group (69%) and placebo (56%). Antacid use was highest in the placebo group. In a systematic review on intermittent and on-demand therapy with PPIs and H2RAs, three studies evaluated patients with NERD. Intermittent therapy with any agent was not effective in NERD or ERD; however, on-demand therapy with H2RAs or PPI provided symptom control in a proportion of patients with NERD [160]. In a meta-analysis of 17 studies, on-demand therapy with PPIs was effective for long-term management of patients with NERD (five studies) and uninvestigated GERD (two studies), but not for patients with erosive GERD [161]. In the Cochrane review on maintenance treatment of GERD, the only RCT in patients with NERD showed superiority of low-dose omeprazole over placebo [162]. For patients who improve on double-dose PPI, stepping down to single dose for maintenance treatment can be successful in 80% patients [163]. Overall, up to 50% patients with mild GERD/NERD will remain asymptomatic off any therapy, indicating that a proportion of such patients after improvement with PPI can be off therapy, and if recurrences occur can be managed with low doses of PPI or H2RA.

38. For maintenance therapy in severe erosive esophagitis, long-term PPI should be offered.

Voting percentage: A 68, B 24, C 4, D 4
Level of evidence: I
Grade of recommendation: A

In the landmark trial on five maintenance therapies in patients with ERD (cisapride, ranitidine, omeprazole, ranitidine + cisapride, and omeprazole with cisapride), the proportion of patients in remission at one year was significantly higher (> 80%) in the omeprazole group (with or without cisapride) than in the H2RA (49% to 66%) or prokinetics (54%) groups [164]. Omeprazole was superior across all grades of esophagitis. In two similar RCTs on patients with ERD who improved with lansoprazole (30 or 15 mg), maintenance/step-down with 30 mg and 15 mg lansoprazole was superior to ranitidine in terms of endoscopic relapse, with no difference between two doses of lansoprazole [165, 166]. In the Cochrane review on maintenance treatment in patients with healed esophagitis, both healing and maintenance doses of PPI were superior to placebo and H2RAs for prevention of relapse; the healing dose, though superior to maintenance dose, was associated with higher chances of adverse events [162]. H2RAs were also superior to placebo and could be considered in PPI-intolerant patients. In another Cochrane review on patients with NERD or mild ERD, on-demand PPI, though inferior to daily PPI in terms of symptom control and patient satisfaction, was associated with lesser pill burden [167]. However, this review commented about inadequacy of data regarding long-term benefits and harm of PPI reduction or discontinuation.

39. In the presence of esophageal strictures, long-term daily PPI maintenance therapy should be given.

Voting percentage: A 84.2, B 13.1, E 2.6
Level of evidence: I
Grade of recommendation: A

The RCTs comparing PPI vs. H2RAs in patients with GERD-associated esophageal stricture have shown that long-term PPI use over a year is better than H2RA in terms of endoscopic healing, dysphagia grades, and need for re-dilation [168–170].

40. In patients with nocturnal reflux symptoms, optimizing PPI therapy or adding an H2RA at night should be considered.

Voting percentage: A 79.2, B 20.8
Level of evidence: II-2
Grade of recommendation: C

Optimizing the PPI therapy may be the first strategy in patients who experience nocturnal reflux symptoms. Although single-dose morning PPI achieves good daytime pH and symptom control, nocturnal pH control remains inadequate, and this can be improved with evening dose of PPI as shown in a healthy volunteer study [171]. However, even on twice-daily PPI dose, patients with GERD may experience symptoms at night, which may or may not be attributed to NAB, defined as gastric pH below 4 for more than one continuous hour at night time in subjects on PPIs [172]. NAB occurs in more than 75% patients with GERD and in normal subjects as well [173]. Addition of bedtime H2RAs in normal volunteers has been shown to reduce nocturnal gastric acidity and NAB [174]. Similarly, addition of bedtime H2RA to double-dose PPI in patients with GERD increased the percentage time when intragastric pH was > 4 from 55% to 97%. The PPI-with-H2RA group had lesser frequency of NAB (40% vs. 82%) and shorter duration of esophageal acid exposure (18 vs. 42 min) than the PPI-only group [175]. In another study, NAB was detected in 64% of patients on twice daily PPI as compared to only 17% in patients with additional night time H2RA [176]. However, there are concerns about tachyphylaxis associated with H2RA, as shown in a study of 23 healthy volunteers and 20 GERD patients. Although PPI + H2RA combination reduced NAB, the effect weaned over one week, highlighting the tolerance associated with continued H2RA therapy [175]. Other studies have doubted the clinical significance of NAB and have found no correlation between esophageal acid exposure and NAB [48, 97, 177]. Therefore, patients having nocturnal symptoms may benefit from optimization of PPI therapy or addition of bedtime H2RA depending upon patients' tolerance, and NAB may or may not correlate with nocturnal esophageal acid exposure or nocturnal symptoms.

41. If there is a partial response to once-daily PPI, increasing the dose of the same PPI to twice daily, or switching to another PPI at once-daily dose, may be considered.

Voting percentage: A 84, B 16
Level of evidence: I
Grade of recommendation: A

Ten percent to 40% patients with GERD have partial or no response to a standard dose of PPI [178]. Given the complex pathophysiology of GERD, this group of patients with no/partial response is heterogeneous, comprising of patients with heartburn of other etiologies, esophageal motility disorders, functional heartburn, or functional chest pain. A third may have abnormal pH test, and the predictors of persistent symptoms include longer duration, associated hiatus hernia, obesity, and suboptimal use of PPI. Only up to 60% patients are adherent to treatment, and up to 46% patients take PPI at appropriate time [179]. In patients with NERD or ERD, in the absence of alarm features, doubling the dose of PPI or switching to another PPI may be tried, if the patient has partial response to a 4-week course of standard dose-optimized PPI. In an RCT of 282 patients with persistent symptoms of heartburn on lansoprazole 30 mg/day, switching to esomeprazole 40 mg/day or increasing the dose of lansoprazole to 30 mg twice daily led to similar improvement in symptom scores and percentage of heartburn-free days, with a small incremental benefit [180]. Thus, doubling the dose of PPI leads to only a modest benefit, with a number needed to treat to benefit of 25 [181].

42. Prokinetics have no proven role in routine management of GERD.

Voting percentage: A 65.2, B 34.8
Level of evidence: II-2
Grade of recommendation: C

Although prokinetics may theoretically 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 northern India, addition of mosapride to PPI was not effective in symptom control in patients with NERD and healing in patients with ERD [182]. However, patients with erosive esophagitis had a better symptom control with combination therapy. 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 [183]. A subset of patients with GERD who have delayed gastric emptying may benefit from the addition of prokinetics [184–186]. Given the adverse effect of many prokinetics on cardiac function, these drugs should be used judiciously [187].

Baclofen, a GABA B agonist, can relieve GER by decreasing the incidence of transient LES relaxation. In a meta-analysis of nine studies (283 patients), baclofen resulted in a short-term decrease in the number and average length of reflux episodes. However, the sample size of individual studies was small, and larger well-designed studies are required for better conclusions [188].

43. Nonresponders to 4 weeks of PPI therapy should be further evaluated.

Voting percentage: A 84, B 8, C 8
Level of evidence: I
Grade of recommendation: A

In a meta-analysis, the pooled response rate on PPIs at 8 weeks (0.50 [95% CI 0.43–0.57]) in patients with uninvestigated GERD was similar to that at 4 weeks (0.47 [95% CI 0.43–0.51]). Therefore, in patients on empiric trial of optimal PPI dose and timing, extension of PPI beyond 4 weeks in nonresponders is unlikely to increase the response rate, and these patients should undergo further diagnostic evaluation apart from causes pertaining to persistent acid exposure, nonacid reflux, heartburn of other etiologies, esophageal motility disorders, functional heartburn, and functional chest pain [189].

Atypical GERD

44. In suspected reflux chest pain syndrome, twice-daily PPI therapy may be given as an empirical trial for 4 weeks, after a cardiac illness has been ruled out.

Voting percentage: A 52, B 44, C 4
Level of evidence: I
Grade of recommendation: A

GERD is the most common cause of noncardiac chest pain. This has led to PPI trial being used as diagnostic test for patients with reflux chest pain syndrome. In a meta-analysis of six studies, overall sensitivity and specificity of a PPI test were 80% and 74%, respectively [190], indicating that such an approach may be used both for diagnostic and therapeutic purposes. In another meta-analysis of seven studies (all except one used double-dose PPI), there was significant improvement in the PPI arm as compared to placebo, with a pooled risk ratio of 0.54 (0.41–0.71) toward continued chest pain [191]. However, the response to PPI depends upon the presence or absence of typical GERD symptoms, as demonstrated in a recent meta-analysis of six RCTs, in which therapeutic gain over placebo was 56% to 85% in GERD-positive, as compared to only 0% to 17% in GERD-negative patients [192].

45. PPIs can be considered in patients with non-seasonal asthma and chronic cough in the presence of typical reflux symptoms.

Voting percentage: A 68.2, B 23.6, C 5.2, D 2.6
Level of evidence: I
Grade of recommendation: B

Twenty-one percent to 41% patients with chronic nonspecific cough (all respiratory causes excluded) can have associated GERD as the cause of cough [193]. In a Cochrane review of 10 RCTs that compared PPI with placebo for treatment of GERD-related cough, only two showed improvement. The overall results did not favor PPI over placebo [194].

Studies on patients with asthma and associated GERD have also revealed heterogeneous results, with some studies showing improvement in forced expiratory volume in the first second (FEV1), peak expiratory flow (PEF), and symptoms [57, 195–198] and others demonstrating negative results [199, 200]. Most studies showing positive results included patients with associated GERD symptoms or positive reflux testing [57, 195, 197]. Therefore, like chronic cough, patients with nonseasonal asthma and associated GERD symptoms may benefit from a PPI trial.

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

Voting percentage: A 87.5, B 12.5
Level of evidence: I
Grade of recommendation: A

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) [201]. However, in a recent network meta-analysis on efficacy and safety of PPIs in patients with NERD, in equipotent doses, all PPIs had similar efficacy for symptom relief [202]. Similarly, in a recent systematic review, neither esomeprazole (26 RCTs, 23,789 patients) nor lansoprazole (13 RCTs, 7532 patients) were different from other PPIs for most outcome measures including efficacy and safety [203].

Adverse events on PPIs

47. Injudicious use of long-term PPIs should be avoided.

Voting percentage: A 92.1, B 7.9
Level of evidence: II-2
Grade of recommendation: A

Long-term use of PPI has been associated with a multitude of adverse events including increased incidence of *Clostridium difficile*-associated diarrhea, bacterial gastroenteritis, community-acquired pneumonia, osteoporosis and increased risk of bone fractures, kidney disease, dementia, and micronutrient malabsorption (calcium, magnesium, and vitamin B_{12}) [204–206]. These conclusions were derived from population-based studies and retrospective analysis, and there are no prospective studies to support these findings [207]. Ten percent to 15% patients with GERD may remain asymptomatic without any treatment and up to a third may do well on H2RA [157, 158]. Therefore, after complete symptomatic relief with PPIs, an effort should be made to stop these, so as to avoid these potential long-

term risks associated with these drugs. A large study of PPI vs. placebo in patients with cardiovascular disease showed no difference between pantoprazole vs. placebo for any of the safety events except for enteric infections (1.4% vs. 1%, OR = 1.33; 95% CI = 1.01 to 1.75). The number needed to harm for enteric infections was 301 (95% CI 152 to 9190) after a median of 3 years of PPI use [208].

Complications

48. The description of Barrett's esophagus on endoscopy should be done using the Prague C and M criteria.

Voting percentage: A 84.5, B 11.5
Level of evidence: II-2
Grade of recommendation: B

The Prague C and M classification system is commonly used for endoscopic standardization of BE [209]. Major academic societies such as the AGA [210], American College of Gastroenterology (ACG) [211], and British Society of Gastroenterology (BSG) recommend the Prague C and M system for reporting BE during endoscopy [212]. According to the Prague system, identifying the following three endoscopic landmarks is of importance: the squamo-columnar junction, GEJ (proximal end of gastric folds), and diaphragmatic hiatus. The circumferential extension (C) between the squamo-columnar junction and GEJ and the maximum length (M) between the most proximal point of the columnar epithelium and the GEJ are measured. Isolated islands of columnar mucosa are not included in the Prague classification, and should be reported separately.

The primary validation study for the C and M criteria was published by Sharma et al. [209], and showed a reliability coefficient of 0.91 (almost perfect) for C and 0.66 (substantial) for M extent (in the internal validation). The external validation study produced a reliability coefficient of 0.94 (95% CI 0.91–0.97) for C and 0.93 (0.89–0.96) for M (almost perfect for both), demonstrating that the new C and M grading system can be easily understood and implemented in routine endoscopic practice.

Regarding the landmark for the GEJ, controversy exists between Japanese and other societies. The BSG, AGA, and ACG recommend the proximal end of the gastric folds as the landmark for the GEJ [210–212] and the same is endorsed in other parts of Asia [213, 214]. Japanese endoscopists use the distal end of the palisade vessels to define the GEJ, which may be anatomically more correct [215]. But the presence of esophagitis and the degree of air insufflation, as well as respiration and peristalsis, tend to make this landmark inconsistent. Thus, the proximal limit of gastric folds is widely accepted as the landmark for the GEJ.

49. Columnar epithelium should extend for more than 1 cm above the proximal gastric fold to call it endoscopically suspected esophageal metaplasia (ESEM).

Voting percentage: A 87, B 13
Level of evidence: II-2
Grade of recommendation: B

In the validation study [209], perfect consistency existed between endoscopists regarding the Prague classification when ESEM extended over one cm. However, for less than one cm of columnar epithelial lining, the reliability coefficient was only 0.22. Endoscopists were unable to recognize or reliably measure the length of BE if it was less than 1 cm. According to British guidelines, 1 cm length of columnar-lined esophagus (M of Prague criteria) was chosen to be the minimum length for an endoscopic diagnosis of BE, in order to distinguish it from an irregular Z line [212]. The Asian Barrett's Consortium also reported excellent interobserver reliability for a Barrett's segment of > 1 cm when using the Prague C and M criteria for grading of BE. The interobserver reliability was low for segments < 1 cm [213]. The consensus is therefore not to accept lesions smaller than 1 cm as BE, when using the Prague system due to its clinical insignificance and the lack of consistency among endoscopists. The use of acetic acid (3% spray) during white light endoscopy enhances the surface pattern and early loss of acetowhitening effect can delineate areas with high-grade dysplasia (HGD) in BE. This is an inexpensive and easily available technique [216]. The use of NBI during endoscopy can also help to identify dysplasia with a high degree of accuracy [217].

50. Patients with esophageal biopsies showing columnar metaplasia are said to have BE.

Voting percentage: A 80, B 16, C 4
Level of evidence: II-2
Grade of recommendation: B

Endoscopically suspected esophageal metaplasia must be confirmed with histological evidence of columnar epithelium for the definitive diagnosis of BE. The presence of intestinal metaplasia (IM) as a diagnostic prerequisite remains controversial [210–212]. The ACG 2011 guidelines require the presence of IM for the diagnosis of BE [210]. The rationale behind this is its greater risk for progression to carcinoma in earlier studies [218–220]. In contrast, the British [212] and Japanese [221] guidelines do not require IM for the diagnosis of BE. The earlier Asia–Pacific consensus [222] required the presence of IM for the diagnosis of BE; this was changed in the 2016 consensus [29].

The rationale for removing IM as a diagnostic criterion is the confounding effect of mucosal biopsy sampling bias on diagnosis. A study that examined the diagnostic yield of IM in patients with known BE found that the optimum number of biopsies to diagnose IM was 8, with an yield of 67.9%; if only 4 biopsies were taken, the yield was only 34.7%. There was no increased yield with more than 8 biopsies, unless more than 16 biopsies were performed (100% yield of IM) [223]. Secondly, retrospective studies have shown that nongoblet columnar metaplasia had a similar neoplastic potential for IM [224, 225].

Recent data show that columnar cell epithelium may have intestinal-type immunohistochemical profile even when goblet cells are not identified.

51. The presence of dysplasia should preferably be confirmed by an experienced pathologist.

Voting percentage: A 69.6, B 21.7, C 4.3, D 4.3
Level of evidence: II-2
Grade of recommendation: A

There is considerable interobserver variability among pathologists in the interpretation of dysplasia in BE. For HGD and esophageal adenocarcinoma (EAC), there is reasonable interobserver agreement among GI pathologists [226]. But substantial difficulty lies in the interpretation of indefinite dysplasia and low-grade dysplasia (LGD) [227]. A recent study showed that, of 147 patients diagnosed with LGD in the community, 85% were downgraded to no-dysplasia after review by two GI pathologists who had extensive experience in the diagnosis of BE-related neoplasia [228]. The same group had the biopsies of an additional 293 patients with LGD diagnosed in the community reviewed by at least two GI pathologists. They found that 73% could be downgraded to indefinite dysplasia or nondysplastic BE [229]. Some studies suggest that community-based pathologists, who may be inexperienced in diagnosis of BE, have difficulties in the interpretation of both nondysplastic BE and dysplasia [230]. Therefore, all readings of dysplasia should be confirmed by a pathologist with extensive experience in the interpretation of Barrett's-associated neoplasia.

52. There is no study from India to support routine surveillance in patients with non-dysplastic Barrett's esophagus.

Voting percentage: A 69.6, B 30.4
Level of evidence: II-3
Grade of recommendation: A

The incidence of EAC has dramatically increased in recent decades, particularly in the West [231]. In the study by Epari and Cade the overall 5-year survival was 47%, and stage-specific 5-year survival was 100%, 71%, 41%, and 21% for stages 0, 1, 2, and 3, respectively [232]. The best hope for improved survival of patients with EAC remains the detection of cancer at an early and potentially curable stage. BE is the only known precursor for EAC. Endoscopic surveillance of patients with BE is the only option available for early detection. While the presence of dysplasia is a firm justification for regular surveillance, nondysplastic BE has a low risk of progression to EAC. Transition from nondysplastic BE to LGD, HGD, and EAC was 0.019, 0.003, and 0.004, respectively, per 1000 person-years in a large meta-analysis by Qiao et al. [233].

India has a low incidence of EAC. But the increasing prevalence of risk factors for EAC, such as smoking, obesity, and diabetes, in India suggests the potential for a similar increase in EAC incidence. A 16-year trend study in EAC from Tamil Nadu, India showed that the trend of increasing incidence in developed countries is not yet seen in India; but most of the patients with adenocarcinoma were males younger than 40 years [234]. The question whether routine surveillance of nondysplastic BE in India is cost-effective is difficult to answer. EAC detected at an earlier stage had better survival [235–241]. A population-based study from the USA did not show any survival benefit from surveillance [242]. It is recognized that surveillance will not be cost-effective for the majority of patients in Asia [243]. The best strategy for surveillance would be selecting patients at higher risk.

53. BE should be excluded by repeat endoscopy, after 8 weeks of PPI treatment, in patients with severe erosive esophagitis (LA grades C and D).

Voting percentage: A 91.3, B 4.3, C 4.3
Level of evidence: II-2
Grade of recommendation: A

Dysplasia detected on pathological examination at the time of BE diagnosis serves as a surrogate marker for risk of progression to EAC and is an indication to plan preventive management and endoscopic surveillance. The presence of HGD entails therapeutic management, while LGD warrants aggressive surveillance. Hence, an accurate assessment of the presence of BE as well as dysplasia is of utmost importance.

The pathological diagnosis of BE is influenced by a number of factors like poor adherence to biopsy protocols, sampling error, and overlying erosive esophagitis [244]. The presence of erosions or ulcers in the esophagus leads to difficulty in recognizing columnar mucosa, if present. Therefore, BE, especially short segment, can be missed if there is associated erosive esophagitis. In a large study, in patients with esophagitis and no BE on initial examination, 9.9% were found to have suspected BE on repeat examination, vs. 1.8% of patients with no esophagitis [245]. In another study, BE was detected in 12% of patients on repeat endoscopy after PPI therapy [246].

Various trials have shown that 8 weeks of PPI therapy is adequate for mucosal healing in most patients with erosive esophagitis [247, 248]. On the basis of these data, a repeat endoscopy after a minimum 8-week course of PPI therapy is recommended prior to screening for BE in patients with grade C and D esophagitis.

Peptic stricture

54. Patients with peptic stricture should receive continuous PPI to reduce the need for repeated dilatation.

Voting percentage: A 92.3, B 7.7
Level of evidence: II-1
Grade of recommendation: A

Peptic strictures result from severe chronic reflux esophagitis and are rare now. The prevalence of strictures is highly variable, ranging from 1% to 2% among patients with GERD seeking medical evaluation [249, 250]. PPI combined with dilation is a logical approach to peptic strictures. PPI decreases grade of dysphagia, frequency of dilation, and the interval between dilations. PPIs are also superior to H2RA in this situation [170, 251].

Endoscopic management

55. Endoscopic antireflux procedures are evolving therapeutic modalities for a select group of patients with GERD.

Voting percentage: A 80, B 12, C 8
Level of evidence: II-2
Grade of recommendation: B

Endotherapy in PPI-dependent GERD is an established treatment modality with good evidence. Systematic reviews and meta-analyses of controlled and prospective cohort efficacy studies of endoscopic radiofrequency therapy showed that the Stretta procedure significantly improves subjective and objective endpoints and therefore should be considered as a viable alternative in managing GERD. Twenty-eight studies (4 RCTs, 23 cohort studies, 1 registry) representing 2468 patients undergoing the Stretta procedure were included in a meta-analysis. The unweighted mean follow up time was 25.4 (14.0, 36.7) months. The pooled results showed that the procedure reduced (improved) the HR-QoL score by −14.6 (−16.48, −12.73; $p < 0.001$). Stretta also reduced the pooled heartburn standardized score by −1.53 (−1.97, −1.09; $p < 0.001$). After Stretta, only 49% patients using PPI at baseline required PPI on follow up. It reduced the incidence of erosive esophagitis by 24% and reduced esophageal acid exposure by a mean of −3.01 (−3.72, −2.30; $p < 0.001$). LES basal pressure, increased by a mean of 1.73 (−0.29, 3.74) mmHg [252]. In an interim analysis of a randomized trial, Stretta was effective in the management of refractory GERD [253]. One-year follow up after endoscopic full-thickness plication showed the procedure to be safe with improvement in objective and subjective parameters (esophageal manometry and impedance/pH monitoring), without the drawbacks of laparoscopic fundoplication. There is a lack of long-term data regarding the efficacy of Stretta. A study comparing Stretta with fundoplication and PPI therapy is desirable. Further studies on the clinical merit of this procedure in specific patient populations such as those refractory or PPI-dependent with small hiatus hernia (< 3 cm) and high volume reflux on pH impedance studies are warranted [254].

Surgical management

56. Surgery for GERD is an effective alternative to long-term medical therapy and should be offered to appropriately selected patients.

Voting percentage: A 54.2, B 37.5, C 8.3
Level of evidence: I
Grade of recommendation: A

The first line of management for GERD is always medical therapy. Surgical management is reserved for patients with complications of reflux such as recurrent or refractory esophagitis, peptic stricture, and BE, persistent reflux symptoms despite acid suppression, and high-volume reflux. Others who are eligible for surgery are those intolerant to PPI, are noncompliant, or are medication-dependent and unwilling to take long-term medication, and those with extraesophageal symptoms (asthma, cough, hoarseness) [255, 256]. The most frequent indication for antireflux surgery is severe GERD nonresponsive to optimal medical therapy that includes both drug therapy and lifestyle modifications [257].

Once surgery is indicated, laparoscopic surgery performed by an experienced surgeon offers significant advantages over open surgery, with similar efficacy and safety. A meta-analysis of 12 prospective trials found 65% reduction in complication rates in patients treated with laparoscopic antireflux surgery compared with open antireflux surgery [258]. Patients undergoing laparoscopic surgery had faster convalescent rate (three fewer days in hospital), faster return to work (8 days sooner), and similar treatment outcome. Laparoscopic Nissen fundoplication (360°) remains the gold standard; for patients with esophageal motility disorders, a 270° posterior fundal wrap is preferred.

57. Patients referred for surgery should undergo preoperative evaluation for esophageal motility and confirmation of GERD.

Voting percentage: A 77.3, B 18.2, E 4.5

Level of evidence: I

Grade of recommendation: A

There is no consensus on the optimal preoperative investigations for appropriate surgical candidates. Minimal investigations include an upper GI endoscopy, esophageal manometry, 24-h pH impedance monitoring, and assessment of esophageal length and degree of hiatal hernia. Some patients may require gastric emptying studies if preoperative symptoms of bloating are present [259].

Upper GI endoscopy not only helps diagnoses GERD but also rules out malignancy and premalignant conditions. Esophageal manometry is not always mandatory in patients with proven GERD (grade C and D esophagitis, BE, or prior pH metry showing high acid exposure) [260, 261]. In patients with persisting esophageal symptoms despite acid suppression, Herregods et al. [262] reported that at least 30% have an alternate diagnoses including functional heartburn, rumination syndrome, and achalasia rather than GERD. In this

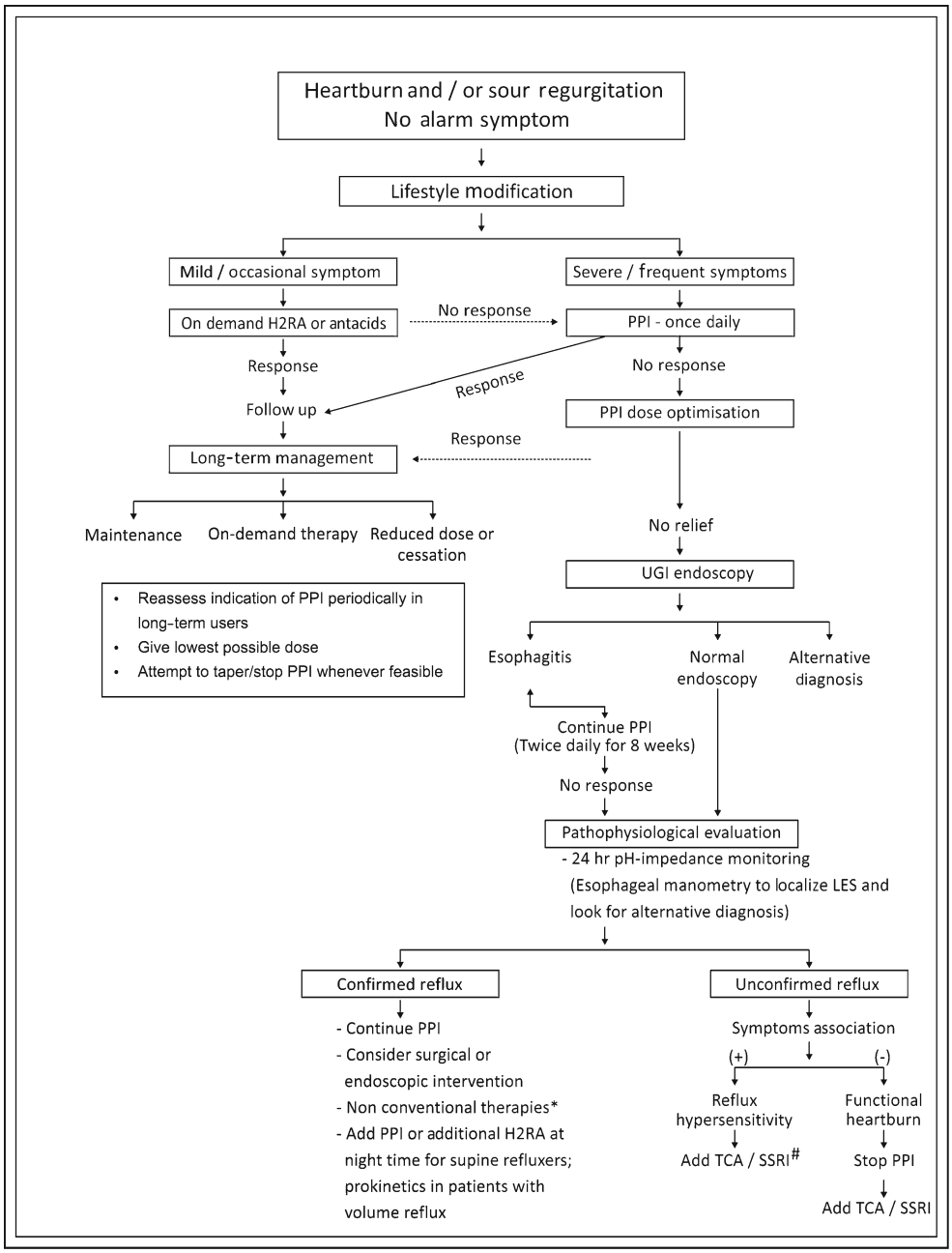

Fig. 1 Management algorithm for GERD. * Nonconventional therapies: These include liquid alginate preparation and TLESR (transient lower esophageal sphincter relaxation) inhibitor baclofen. # A formal psychiatry consultation may be helpful to rule out any major psychiatric comorbidity

PPI proton pump inhibitors, *UGI* upper gastrointestinal, *LES* lower esophageal sphincter, *H2RA* histamine H2 receptor blockers, *TCA* tricyclic antideprssant, *SSRI* selective serotonin reuptake inhibitor

setting, manometry serves an important function to exclude achalasia and other severe motility disorders prior to antireflux surgery. 24-h pH impedance metry may be indicated to confirm GERD and to detect nonacid and high-volume reflux [259]. Barium swallow may be indicated in patients with large hiatal hernia and to identify short esophagus.

58. Surgery should be avoided in patients of GERD with gastroparesis.

Voting percentage: A 82.6, B 17.4
Level of evidence: II-1
Grade of recommendation: A

Approximately 20% to 40% of patients with GERD have associated symptoms suggestive of delayed gastric emptying [263]. In patients with GERD and gastroparesis, antireflux surgery may be followed by severe nausea, vomiting, or gas bloat. There are also concerns about poor outcomes (unhappy patients) or wrap disruption. Gastric emptying studies (for solids and liquids) should be considered when the careful history during evaluation of GERD suggests gastric outlet obstruction or gastroparesis. Patients need to be counseled about postoperative bloat and discomfort and about the need for revision surgery or addition of pyloroplasty [263]. Alternatively, these patients may instead be treated with radiofrequency ablation of the cardia and EGJ [264].

Conclusions

This is the first consensus on GERD from India. We have summarized existing data from India and suggested guidelines based on these data. Where data from India were not available, guidelines from the Asia–Pacific region and, in some cases, European and American guidelines have been discussed. This report shows that there are similarities and differences between India, Asia–Pacific, and the Western world in the management of GERD.

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 (Fig. 1). Testing to prove GERD (pH-impedance metry) and exclude disorders that can mimic GERD (e.g. manometry to exclude achalasia) should be done before patients are subjected to surgical treatment.

Author contributions AKD, SJB, UCG, VA, KD, and GVR generated the initial list of statements. AJ coordinated with the responders for the second round of voting. AKD, AJ, UCG, SK, KD, RD, and RK presented the evidence in seven parts at the final face-to-face meeting. Other members of the ISG Task Force voted in all the three rounds. All authors approved the manuscript.

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Compliance with ethical standards

Conflict of interest SJB, GKM, PA, NB, AK, DNR, UCG, VA, GVR, KD, AKD, AJ, SK, RD, RK, JFA, SD, VKD, MKG, BDG, SKI, VL, MKM, PM, PM, SN, CGP, LP, AVSP, DS, JSS, RS, JV, VM, AB, UD, AKJ, RK, ASP, SPS, LS, AS, and RTW declare that they have no conflict of interest.

Ethical statement The study was performed in a manner to conform with the Helsinki Declaration of 1975, as revised in 2000 and 2008 concerning human and animal rights, and the authors followed the policy concerning informed consent as shown on Springer.com.

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