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Guidelines

Italian guidelines for the diagnosis and management of gastro-esophageal reflux disease: Joint consensus from the Italian Societies of: Gastroenterology and Endoscopy (SIGE), Neurogastroenterology and Motility (SINGEM), Hospital Gastroenterologists and Endoscopists (AIGO), Digestive Endoscopy (SIED), and General Medicine (SIMG)

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ABSTRACT

Gastroesophageal reflux disease (GERD) is one of the most common conditions encountered in outpatient general medicine and gastroenterology clinics. However, uncertainties remain, particularly concerning the optimal diagnostic work-up and the most effective management. To address this issue, experts from 5 Italian Societies conducted a Delphi consensus process, which included a review of the current literature and voting process on 27 key statements. Recommendations and quality of evidence were evaluated using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) criteria. Consensus for each statement was defined as ≥ 80 % agreement.

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Keywords:
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Diagnostic Approach: The consensus supports a symptom-based diagnostic strategy for GERD, focusing on the exclusion of alarm symptoms and/or multiple risk factors for Barrett's esophagus or eosinophilic esophagitis (EoE) as well as non-GERD causes in cases of extra-esophageal symptoms. Esophago-gastroduodenoscopy (EGD) is recommended in patients with alarm features or in patients unresponsive to proton pump inhibitors (PPIs). In addition, the consensus recommends esophageal pH-metry or impedance-pH recording in patients with reflux-like symptoms not responding to medical treatments, in those with extra-oesophageal symptoms, prior to anti-reflux endoscopic or surgical procedures, in patients with belching disorders and to diagnose functional heartburn (FH) and reflux hypersensitivity (RH) in PPI-refractory patients.

Treatment Approach: The consensus strongly supports a standard 4–8 weeks course of PPIs for patients with heartburn and regurgitation but without alarm symptoms and an 8 weeks treatment for those with erosive oesophagitis. Twice daily dose PPIs is recommended only if a concomitant Barrett oesophagus is present, in patients with laryngopharyngeal reflux disease (LPRD) or when there is no response or an incomplete response to once daily dose. Bedtime histamine-2 receptor antagonists (H_2RAs) as add-on therapy is suggested in patients with persistent nocturnal symptoms and in those with objective evidence of nocturnal acid reflux on pH monitoring despite PPI treatment, while prokinetic agents are advocated as add-on therapy in patients with concomitant symptoms suggestive of delayed gastric emptying. Moreover, the consensus voted for the use of potassium competitive acid blockers (P-CABs), antacids, alginate-containing formulations, neuromodulators in treating visceral hypersensitivity, complementary and alternative medicine and anti-reflux surgery in patients with refractory GERD. Finally, the consensus voted against surgical anti-reflux therapy in patients with extra-esophageal symptoms of GERD, who do not respond to PPI therapy and against the use of ensoscopic procedures [i.e., Medigus ultrasonic surgical endostapler (MUSE), radiofrequency energy application (Stretta), anti-reflux mucosectomy (ARMS)] outside clinical trials.

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1. Introduction

Gastroesophageal reflux disease (GERD) is defined as the presence of symptoms or mucosal damage produced by the abnormal reflux of gastric contents into the esophagus or beyond, i.e., into the oral cavity or upper airways.

GERD can be classified as non-erosive reflux disease (NERD) or erosive reflux disease (ERD) based on the presence or absence of esophageal mucosal damage at endoscopy [1,2].

GERD can manifest in a wide range of symptoms which can be subdivided into typical, atypical and extra-esophageal symptoms [3–6].

In general, symptoms tend to be more common after meals and are often aggravated by recumbency and relieved by antacids, alginate-containing formulations or acid lowering medications [7]. Typical symptoms such as heartburn and acid regurgitation have high specificity but low sensitivity for GERD [8].

On the other hand, gastric symptoms including epigastric pain, epigastric burning, nausea, bloating, and belching may be suggestive of GERD but overlap with other conditions such as peptic ulcer disease, gastritis, functional dyspepsia and gastroparesis [9–13]. Lastly, various extra-esophageal symptoms including chronic cough, asthma, hoarseness and dental erosions may be present [14].

Despite its high prevalence, GERD is associated with major uncertainties, especially regarding its optimal diagnostic work-up and its targeted and more appropriate management. Consequently, a joint group of experts of the Italian Societies of Gastroenterology and Endoscopy (SIGE), Neurogastroenterology and Motility (SINGEM), Italian Association of Hospital Gastroenterologists and Endoscopists (AIGO), Digestive Endoscopy (SIED) and General Medicine (SIMG) found it worthwhile to develop updated clinical practical guidelines to increase the awareness of this disorder and support clinicians in the diagnosis and management of patients, in order to optimize clinical outcomes.

2. Methods

The SIGE proposed the current guidelines about the management of GERD. Representatives' members of SIGE, SINGEM, AIGO, SIED and SIMG participated to the Delphi process to develop consensus statements on the diagnosis and treatment of GERD. The Delphi process is based on the principles of evidence-based medicine and consists of a systematic search of the literature, the production of statements based on the best available evidence, and a voting process in order to determine consensus, especially for those fields of medicine not supported by evidence from controlled trials [15]. Each statement produced reported the quality of available evidence and the strength of the recommendation according to the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system [16]. At the end of the Delphi process, three experts (Carmelo Scarpignato, Vincenzo Savarino and Vincenzo Stanghellini) in the field (>250 papers published), revised the statements, the supporting evidence, and the strength of recommendation as external reviewers.

The Core Working Group, composed by 4 panel members (EVS, GS, BB and MP) with expertise in GERD and/or Delphi consensus processes and/or guidelines [17–21], identified 27 clinical questions to answer using the patient, intervention, control, and outcome (PICO) process (Supplementary Table 1). The Italian Consensus Group was recruited within the SIGE and other Italian societies in the field of Gastroenterology and included experts in GERD. All members submitted a conflict-of-interest statement by June 2023. All panel members performed a systematic literature review to answer each PICO and drafted statements with a summary of the evidence. Grading of the strength of recommendation was performed using accepted criteria and finally, one to two rounds of repeated voting of the statements were performed until a consensus was reached.

The literature search was performed using MEDLINE, EMBASE, Web of Science and the Cochrane Database of Systematic Reviews until June 30th 2023, without time and/or language restrictions. References were available in an online shared folder accessible

Table 1
Six-point Likert scale.

point	Description
A+	agree strongly
A	agree with minor reservation
A-	agree with major reservation
D-	disagree with major reservation
D	disagree with minor reservation
D+	disagree strongly

to all members. Researchers prioritized data from systematic reviews and meta-analyses of randomized controlled trials (RCTs), when available. The strength of recommendation (GR) was assessed using the GRADE methodology [22] and the recommendations for each different clinical scenario were classified into three categories: strong (desirable effects outweigh undesirable effects), conditional (trade-offs are less certain) or consensus (the expert opinion supports the guideline recommendation even though the available scientific evidence does not present consistent results, or controlled trials are lacking).

To evaluate the quality of evidence (LE: Level of Evidence), the following definitions were used: high (further research is unlikely to change confidence in the estimate), moderate (further research is likely to change confidence in the estimate), low (further research is very likely to change confidence in the estimate), or very low (the estimate of the effect is very uncertain). The quality of the evidence could be downgraded or upgraded according to different factors such as limitations or implementations in the study design, imprecision of estimates, variability in the results, indirectness of the evidence, publication bias, large magnitude of effects, dose-response gradient, or if all the plausible biases would reduce an apparent treatment effect. In addition, the recommendations also considered other factors such alternative management strategies, variability in values and preferences and the costs.

The finalized statements with the summary of evidence were edited and discussed in a 3-day online session. Thereafter, all members were asked to participate in a first blinded voting round in September 2023 to give their agreement with the statements using a 6-point Likert scale (Table 1) and to provide feedback on their clarity. When at least 80 % of the members agreed with a given statement (A+ or A), this was defined as consensus. Since the agreement on all statements was reached after the first voting round, the manuscript was drafted and reviewed by participants for final approval. The final document was then submitted for external review to improve the quality of the guidelines.

3. Results

SECTION 1: Diagnosis (Fig. 1a and Fig. 1b, Table 2)

Statement 1.1: The Panel recognizes that GERD should be suspected when patients refer heartburn and/or regurgitation twice or more weekly.
Statement endorsed, overall agreement: 100 %: *A* + 60.87 %, A 39.17 %, A- 0 %, D- 0 %, D 0 %, *D*+ =%.
LE: Conditional recommendation, moderate level of evidence.

Summary of evidence: Typical symptoms of GERD include heartburn and regurgitation. Heartburn is the most common GERD symptom and is described as substernal burning sensation rising from the epigastrium up toward the neck. Regurgitation is the effortless return of gastric contents upward toward the mouth, often accompanied by an acid or bitter taste. Although both heartburn and regurgitation are major symptoms of GERD, the genesis of these symptoms is not the same, and the diagnostic and management approaches vary depending on which symptom predominates [23].

In the Montreal Consensus era many clinical trials defined GERD by the presence of two mild episodes of heartburn per week and as high as five daytime episodes and one night-time episode per week as minimal entry criteria for GERD diagnosis [24]. This threshold was suggested based on a population-based study in Sweden, in which heartburn that was mild or worse was associated with a clinically meaningful reduction in well-being [24]. Data for symptom frequency come from a population-based study of two communities in northern Sweden [25]. Mild symptoms on two or more days a week were associated with a significant reduction in quality of life measured by a disease-specific instrument [25].

Statement 1.2: The Panel recognizes that GERD is objectively defined by the presence of characteristic mucosal injury seen at endoscopy and/or abnormal oesophageal acid exposure demonstrated on a reflux monitoring study.
Statement endorsed, overall agreement: 100 %: *A* + 60.87 %, A 39.17 %, A- 0 %, D- 0 %, D 0 %, *D*+ =%.
LE: Conditional recommendation, high level of evidence.

Summary of evidence: The pathophysiology of GERD involves many different mechanisms, including components of the esophagus itself and the disruption of esophago-gastric junction (EGJ). Accordingly, there is evidence that ineffective esophageal clearance, impaired esophageal mucosal defence, abnormalities of lower esophageal sphincter (LES) function, mainly the transient LES relaxations (TLESRs) and a reduced LES pressure, all can contribute to the development of GERD [26–31]. Gastroesophageal refluxate contains a variety of noxious agents, including acid, pepsin and bile, and when esophageal defensive factors are unable to cope with these substances, esophageal cell damage and troublesome symptoms can result [26,32,33].

GERD diagnosis based on the presence of typical symptoms was suggested during Montreal consensus [34]. However, it must be emphasized that a diagnosis based exclusively on symptoms is poorly accurate, because it has a 70 % sensitivity and a 67 % specificity, when compared with objective evidence of GERD defined by esophageal pH-metry and/or upper endoscopy [35]. Indeed, the above typical symptoms can be associated with esophageal diseases other than GERD, such as achalasia, eosinophilic esophagitis (EoE) or functional heartburn (FH) [36,8,37–41].

A short (4- to 8-week) course of proton pump inhibitor (PPI) treatment is a practical approach for patients presenting with reflux symptoms. However, it was demonstrated that 51 % of primary care patients with upper gastrointestinal symptoms who responded to PPIs tested negative for GERD. Accordingly, a clinical response to PPIs does not confirm the diagnosis of GERD [35]. In addition, around 50 % of patients who do not respond to PPIs and 20 % of those who respond to PPIs may have FH [42]. Thus, PPI response is not a reliable diagnostic tool, although it can help management and remains the most practical approach in patients with GERD-like symptoms in order to evaluate symptom relief. With these premises, Lyon Consensus 2.0 defined “actionable” GERD or objectively defined GERD as the presence of characteristic mucosal injury seen at endoscopy (erosive esophagitis grade B, C, D or Barrett’s esophagus) and/or abnormal esophageal acid exposure demonstrated on a reflux monitoring study. Moreover, adjunctive metrics that consolidate or refute GERD diagnosis when primary criteria are borderline or inconclusive have been proposed [43].

Statement 1.3: The Panel recommends FOR evaluating non-GERD causes in patients with extra-esophageal manifestations before attributing symptoms to GERD.
Statement endorsed, overall agreement: 100 %: *A* + 60.87 %, A 39.17 %, A- 0 %, D- 0 %, D 0 %, *D*+ =%.
LE: Strong recommendation, moderate level of evidence.

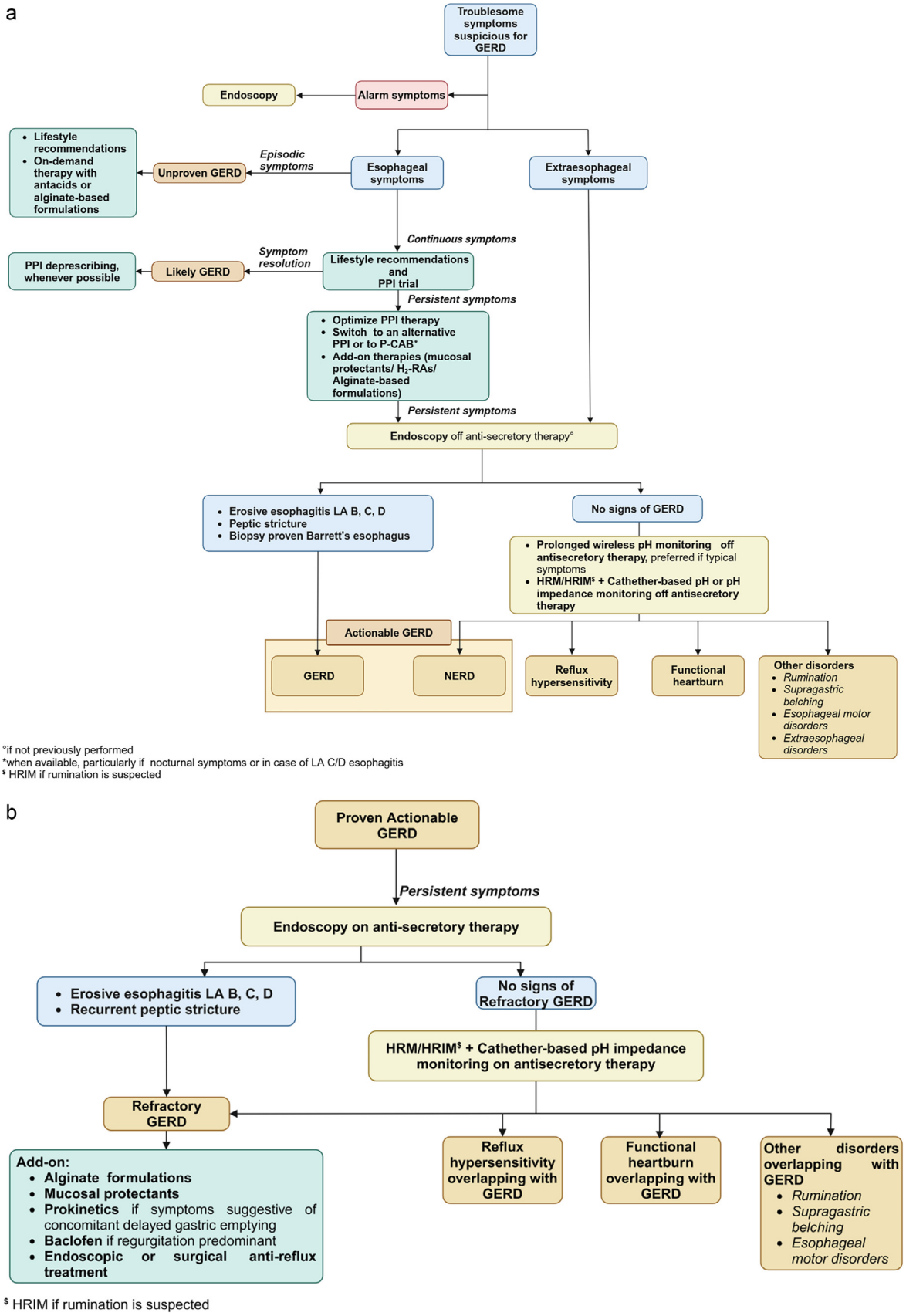

Fig. 1. (a–b). Diagnostic and therapeutic algorithms for GERD. (a) Initial evaluation and management of suspected GERD. (b) Work-up and treatment of persistent symptoms in proven actionable GERD.

Summary of evidence: The association between GERD and extra-esophageal symptoms has been examined in multiple studies. In a case-control study of veterans, patients with esophagitis or esophageal strictures were more likely to have a diagnosis of laryngitis (OR 2.01), aphonia (OR 1.81), asthma (OR 1.51), and pharyngitis (OR 1.48) compared with control patients [44]. In a US survey study, 26 % of patients reported both GERD and laryngeal symptoms [45]. Of this group with both GERD and laryngeal complaints, 38 % reported voice disorders and 44 % had occasional breathing difficulties. Some studies have suggested that chronic cough may be due to GERD in 21 %–41 % of cases [46]. However, because of the wide variety of causes of chronic cough, the American College of Chest Physicians guideline for evaluation of chronic cough suggests looking for other sources before attributing chronic cough to GERD [47].

GERD may also have a role in asthma, with one systematic review of 28 studies identifying GERD symptoms in 59 % of patients with asthma and abnormal pH testing in 51 % [48]. However, data from several RCTs suggest that PPI treatment is ineffective for many patients with asthma, raising question about the role of acid reflux in asthma symptoms [49–51]. Moreover, GERD has been associated with idiopathic pulmonary fibrosis (IPF) being a frequent comorbidity in these patients, as demonstrated using combined multichannel intraluminal impedance-pH (MII-pH), despite being mostly clinically silent [52–55]. According to that, it has been hypothesized that micro aspiration of gastric material may play a crucial role in the fibrotic transformation of pulmonary parenchyma. In contrast, it cannot be excluded that IPF may favour GERD through the increase in negative intrathoracic pressure. Therefore, this relationship remains uncertain and ambiguous. Nevertheless, the latest international guidelines recommend the use of PPIs in IPF based on several studies showing that PPIs can stabilize lung function, reduce disease flares and hospitalizations [54–57]. Overall, most patients, referred for extra-esophageal symptoms (especially sore throat, hoarseness, throat clearing) or laryngo-esophageal signs of reflux, resulted negative (>60 %) when evaluated with 24 h impedance and pH monitoring test [58]. There is increasing research supporting the reflex theory and hypersensitivity syndrome underlying the pathophysiology of laryngeal symptoms suspected as being GERD related [59,60].

Statement 1.4: The Panel recommends FOR considering disorders of gut-brain interaction as functional heartburn and reflux hypersensitivity in patients with proven GERD and incomplete response to PPIs.
Statement endorsed, overall agreement: 95.65 %: *A* + 78.25 %, A 17.40 %, A- 4.35 %, D- 0 %, D 0 %, *D* + 0 %.
LE: Strong recommendation, low level of evidence.

Summary of evidence: GERD has been associated with various disorders of gut-brain interaction, including FH and reflux hypersensitivity (RH) [36,61]. According to Rome IV [62] criteria the overlap of FH with proven GERD is diagnosed when heartburn persists despite maximal PPI therapy, taken appropriately before meals, in patients with history of proven GERD (i.e., positive pH study, severe erosive esophagitis, Barrett's esophagus, or esophageal stricture), and pH-impendence monitoring ON PPI therapy demonstrating physiologic acid exposure without reflux-symptom association (i.e., negative symptom index - SI - and symptom association probability - SAP) [36,63–65]. Likewise, RH overlaps with proven GERD when heartburn persists despite maximal PPI therapy and pH impedance testing ON PPI therapy demonstrates physiologic acid exposure with positive reflux–symptom association [64,66,67]. Since the concept of overlapping GERD and disorders of gut-brain interaction has been introduced recently, little is known about its prevalence. However, studies performed with 24-hour pH-impedance monitoring report that between 21 % and 40 % of patients with refractory reflux symptoms have FH or RH [68,69]. Recently, Rengarajan and co-workers, showed that FH and RH can be diagnosed both ON and OFF PPI therapy in patients with or without proven GERD, respectively [70]. These findings support the Rome IV working hypothesis that disorders of gut-brain interaction can overlap with proven GERD, with potentially relevant implications for treatment [69,71].

Statement 1.5: The Panel recommends FOR performing oesophageal impedance-pH monitoring ON PPIs for patients with an established diagnosis of GERD whose symptoms have not responded adequately to twice-daily PPI therapy.
Statement endorsed, overall agreement: 95.65 %: *A* + 78.25 %, A 17.40 %, A- 4.35 %, D- 0 %, D 0 %, *D* + 0 %.
LE: Strong recommendation, low level of evidence.

Summary of evidence: Patients with proven GERD (previous evidence of reflux esophagitis, Barrett's esophagus (BE), refractory peptic stricture and/or abnormal pH monitoring) and persistent symptoms should be investigated on double-dose PPI therapy with pH-impedance monitoring, which allows the detection of weakly acidic reflux events [72,73,26]. Moreover, the evaluation of mean nocturnal baseline impedance (MNBI), a surrogate marker of mucosal integrity, and post-swallow reflux induced peristaltic wave index (PSPW-I),which reflects the chemical clearance of refluxate, has been shown to be of help in refining patients with FH or RH when symptoms do not occur during the reflux monitoring carried out OFF or ON PPI therapy [66,74,75]. Overall, on-therapy pH-impedance monitoring can establish a relationship between symptoms and acid reflux or weakly acidic reflux in 10 % and 30 %–40 % of patients, respectively, while negative studies are found in 50 %–60 % of patients [70,76]. Of note, a study published by Penagini and coworkers showed that one-third of patients classified as FH on 24-hour pH-impedance monitoring could be re-classified as NERD after a more prolonged pH recording [77].

Due to the inability to assess non-acid reflux episodes, other tests, such as wireless pH-metry, have limited evidence in differentiating GERD subtypes [78–82]. In particular, although esophageal biopsies have been shown to be useful in identifying patients with FH [83,84], they are not recommended in clinical practice and they could be more important to rule out EoE in the diagnostic workup of refractory GERD [18,19]. In this regard, EoE may be present in a significant proportion of patients, even when the macroscopical appearance of the esophageal mucosa is normal. However, to increase the diagnostic yield of biopsy for EoE, only patients with typical features of eosinophilic disorders (i.e., young age, male gender, history of atopy disease) should be investigated [85–87]. In a multicentre study, only 21 % of patients with persistent heartburn on PPIs were found to have true refractory GERD [88].

Statement 1.6: The Panel recommends FOR using GERD-related questionnaires in clinical practice to evaluate clinical response to an appropriate GERD treatment
Statement endorsed, overall agreement: 91.30 %: *A* + 47.82 %, A 43.48 %, A- 8.70 %, D- 0 %, D 0 %, *D* + 0 %.
LE: Conditional recommendation, moderate level of evidence.

Summary of evidence: A large number of questionnaires have been developed, validated, translated into different languages, evaluated, and compared for assessment of GERD. There are multiple dimensions in the assessment of a specific disease with a questionnaire [89,90]. In GERD, one of the most important dimensions is symptoms, including typical and atypical (i.e., extra-esophageal) symptoms. Another assessment dimension is the response to treatment, in which the change in severity and/or frequency of symp-

toms is measured. A third dimension is diagnosis, a tool to discriminate patients with GERD from other diseases. Finally, the impact of GERD on disease-specific quality of life, reflecting its burden on patients' overall quality of life, is an important dimension in GERD assessment.

However, when compared with objective evidence of GERD defined by pH-metry or endoscopy, even a history taken by an expert gastroenterologist has only 70 % sensitivity and 67 % specificity, highlighting the distinction between a physiology-based and a symptom-based GERD diagnoses [35]. Likewise, questionnaires such as the reflux disease questionnaire (RDQ) and gastroesophageal reflux disease questionnaire (GERDQ), also translated into Italian language, have similar limitations when compared with physiological testing [35,91,92]. Considering these limitations, questionnaires might be used to define clinical response to first line PPI trial. Many international guidelines recommend considering questionnaires as a first-line approach for patients with recurrent GERD symptoms and no alarm symptoms, despite the fact that these questionnaires are neither highly specific nor sensitive [93–96].

A recent meta-analysis estimated high performance scores of artificial intelligence (AI) algorithms in the diagnosis of GERD based on symptoms assessed via questionnaires [20]. However, larger prospective studies are required to establish the utility and applicability of AI in clinical practice.

Statement 1.7: The Panel recommends FOR trying an empiric 8-week trial of PPIs once daily before a meal (30 min before breakfast) for patients with typical GERD symptoms (heartburn and regurgitation) who have no alarm symptoms.
Statement endorsed, overall agreement: 91.30 %: *A* + 78.26 %, A 13.04 %, A- 8.70 %, D- 0 %, D 0 %, *D* + 0 %.
LE: Strong recommendation, moderate level of evidence.

Summary of evidence: PPIs are the most prescribed treatment for GERD. This is based on a large sample of data which showed that PPIs demonstrated higher rates of relief of heartburn and regurgitation, as well as improved mucosal healing compared with H_2RAs [97,98].

PPIs showed a significantly quicker healing rate (12 %/week) versus H_2RAs (6 %/week), and faster and more complete heartburn relief (11.5 %/week vs 6.4 %/week) [99,100].

PPIs are associated with a greater rate of complete symptom relief (usually assessed at 4 weeks) in patients with ERD compared with patients with NERD, with symptom relief of around 70 %–80 %, and 50 %–60 %, respectively [101].

On the other hand, in patients diagnosed with NERD according to pH-impedance monitoring, the estimated symptom response rate after PPI therapy is comparable to that of ERD. The previously reported low response rate in studies with patients classified as NERD is likely the result of inclusion of patients with upper functional gastrointestinal symptoms [102].

A recent systematic review and network meta-analysis evaluating 23 RCTs containing 10,735 subjects with endoscopy-negative reflux disease showed that, based on failure to achieve complete relief of symptoms between ≥2 and <4 weeks, omeprazole 20 mg o.d. (P-score 0.94) ranked first, with esomeprazole 20 mg o.d. or 40 mg o.d. ranked second and third [103]. In achieving adequate relief, only rabeprazole 10 mg o.d. was significantly more efficacious than placebo. For failure to achieve complete relief at ≥4 weeks, dexlansoprazole 30 mg o.d. (P-score 0.95) ranked first, with 30 ml alginate q.i.d. combined with omeprazole 20 mg o.d., and 30 ml alginate t.i.d. second and third. In terms of failure to achieve adequate relief at ≥4 weeks, dexlansoprazole 60 mg o.d. ranked first (P-score 0.90), with dexlansoprazole 30 mg o.d. and rabeprazole 20 mg o.d. second and third [103]. Overall, this analysis confirmed superiority of PPIs compared with most other drugs in treating endoscopy-negative reflux disease.

Other recent clinical guidelines support an initial trial treatment period of once-daily, standard PPI dose for 4 weeks in patients with typical GERD symptoms [68]. If this treatment is successful, the patient should continue with a PPI at the lowest effective dose, as maintenance treatment, provided that continued medication is deemed necessary for a longer period [23].

Statement 1.8: The Panel recommends FOR an empiric PPI trial in patients with extra-esophageal GERD presentation *only* if typical symptoms are present.
Statement endorsed, overall agreement: 91.30 %: *A* + 78.26 %, A 13.04 %, A- 8.70 %, D- 0 %, D 0 %, *D* + 0 %.
LE: Strong recommendation, moderate level of evidence.

Summary of evidence: The PPI treatment has been evaluated to diagnose and treat patients with extra-esophageal symptoms [104,105]. The efficacy of PPIs in laryngo-pharyngeal reflux (LPR) remains unclear. Indeed, some meta-analyses found no significant benefit of PPIs [106–108], whereas 2 others reported some benefit [109,110]. The significant variation in defining LPR, even across different RCTs, makes it challenging to draw clear conclusions in this field. A meta-analysis demonstrating a positive role for PPI treatment highlighted the importance of dietary and lifestyle modifications in improving treatment outcomes [109]. Another systematic review and meta-analysis supported the role of acid inhibition in controlling symptoms although no changes were observed in laryngoscopy findings after treatment [111].

Regarding the management of chronic cough, a systematic review and meta-analysis concluded that PPIs for ~~a~~ GERD-related chronic cough probably have minimal effect in some adults. However, the impact is not as consistent as reported in cohort studies [112].

One RCT demonstrated improved asthma symptoms in patients taking twice-daily PPIs, specifically in those with GERD and nocturnal respiratory symptoms [113].

In conclusion, patients with extra-esophageal symptoms such as chronic cough, sore throat or hoarseness combined with typical symptoms of GERD (heartburn and regurgitation) should be given an initial trial of PPI [114]. Accordingly, the most recent guidelines of the American College of Gastroenterology (ACG) suggested that patients with possible extra-esophageal manifestations of GERD should be evaluated for a different diagnosis before ascribing their symptoms to GERD and that a double dose PPI trial should be prescribed to patients reporting extra-esophageal symptoms reported in combination with frequent (> twice weekly) typical GERD-related symptoms [93].

Statement 1.9: The Panel recommends FOR an ambulatory reflux monitoring before empiric PPI therapy in patients with extraesophageal manifestations of GERD *without* typical GERD symptoms (e.g., heartburn and regurgitation).
Statement endorsed, overall agreement: 91.30 %: *A* + 78.26 %, A 13.04 %, A- 8.70 %, D- 0 %, D 0 %, *D* + 0 %.
LE: Strong recommendation, moderate level of evidence.

Summary of evidence: The accurate identification of patients with laryngo-pharyngeal symptoms potentially caused by GERD is crucial. Exclusion of laryngeal disorders with laryngoscopy is an appropriate first step. If laryngoscopy is negative, there are no accepted guidelines to proceed further in the diagnostic process. The Reflux Symptom Index (RSI) and Reflux Finding Score (RFS) were developed by ENT (Ear-Nose-Throat) specialists to assess laryngo-pharyngeal symptoms and to record laryngoscopy findings in patients with suspected GERD [115]. However, these tools are not reproducible because RSI is not validated and RFS depends on

the experience of the laryngologist who grades it. Milstein et al., found that several signs of posterior laryngeal irritation (i.e., interarytenoid bar, erythema of the medial wall of the arytenoids), which are generally considered to be signs of LPR, are present in a high percentage of asymptomatic individuals, raising doubts about their diagnostic specificity [116]. Accordingly, laryngoscopy should not be used to diagnose GERD and ENT GERD-related findings should be interpreted with caution, with a preference for objective testing (such as EGD or pH-impedance monitoring) to confirm GERD, when necessary [93].

A RCT showed that, in patients with extra-esophageal manifestation of GERD and posterior laryngitis without frequent heartburn, placebo response was better than that of esomeprazole [117]. Chronic cough has also been attributed to GERD, but recent studies and systematic reviews suggested that PPIs are not effective in treating chronic cough in most patients [47,118–120]. If the extra-esophageal symptoms (cough, sore throat, hoarseness, etc.) are not associated with typical GERD symptoms, their aetiology should be firstly considered. Even if GERD is suspected as underlying cause, endoscopy (off PPI treatment) and pH-impedance monitoring should be performed to establish a diagnosis of GERD and drive correct management [93,121,122].

Statement 1.10: The Panel recommends AGAINST routine urea breath testing or *Helicobacter pylori* stool antigen testing in all patients with GERD.
Statement endorsed, overall agreement: 82.61 %: *A* + 73.91, A 8.70, A- 4.35, D- 13.04, D 0 %, *D* + 0 %
LE: Strong recommendation, low level of evidence.

Summary of evidence: Epidemiological studies showed a negative association between the prevalence of *Helicobacter pylori (H. pylori)* infection and the presence and severity of GERD [123]. A review of 26 studies demonstrated a prevalence of *H. pylori* infection in patients with GERD of 39 % compared with 50 % in the control group [124]. Some studies suggested that *H. pylori* strains positive for Cag A (that are strongly associated with the development of corpus gastritis) may be particularly protective against the more severe forms of GERD [125,126]. Likewise, the sequelae of GERD, including BE and esophageal adenocarcinoma, are less common in infected patients [127]. However, eradication of *H. pylori* in populations of infected patients neither causes nor exacerbates GERD [128,129]. In addition, it is recognized that the long-term efficacy of PPI maintenance treatment for GERD is not influenced by *H. pylori* status [130].

Nevertheless, Kuipers et al. found a potential risk for development of atrophic gastritis in infected patients on long-term PPI [131]. However, the lack of evidence of observational data in this regard suggests recommending against routinely screening GERD patients for *H. pylori* infection. It is important to note that if a patient's dominant or most troublesome symptoms are not typical of GERD, other diagnoses should be considered, including *H. pylori*–related diseases, particularly in regions where this infection is highly prevalent [132]. Urea breath testing (UBT; 13C or 14C) or *H. pylori* stool antigen testing are recommended as non-invasive tests for active *H. pylori* infection. This approach serves as the foundation for a 'test-and-treat' strategy in regions where the prevalence of *H. pylori* exceeds 20 % [132]

Statement 1.11: The Panel recommends AGAINST performing routine EGD in all patients with GERD symptoms.
Statement endorsed, overall agreement: 82.61 %: *A* + 65.22 %, A 17.39 %, A- 13.04 %, D- 0 %, D 4.35 %, *D* + 0 %
LE: Strong recommendation, moderate level of evidence.

Empirical diagnosis of GERD must be based on symptoms and confirmed by a favourable response to antisecretory medical therapy [34]. Indeed, in case of typical or uncomplicated GERD, an initial trial of empiric medical therapy is appropriate before considering endoscopy in most patients [133].

Endoscopy at presentation should be considered in patients with symptoms suggestive for complicated disease (dysphagia, odynophagia, unintentional weight loss > 5 %, evidence of gastrointestinal bleeding or anaemia, persistent vomiting). Moreover, it should be considered in patients with multiple risk factors for BE (≥50 years of age, male sex, white race, a family history of BE or esophageal adenocarcinoma, prolonged reflux symptoms, smoking, and obesity) [134].

Other specific cases in which an EGD should be performed in patients with GERD symptoms are: failure to respond to an appropriate antisecretory therapy; finding of mass, stricture, or ulcer on imaging study; preoperative evaluation of patients selected for endoscopic or surgical anti-reflux procedures; presence of recurrent symptoms after endoscopic or surgical anti-reflux procedures; presence of features suggestive of EoE diagnosis (ie. male gender, young age, atopy comorbidities, history of dysphagia or bolus impaction); positioning of wireless esophageal pH monitoring devices [135].

Evidence is lacking to support the routine use of EGD in patients with uncomplicated GERD, who are responsive to medical therapy. The ASGE recommends that once-in-a-lifetime EGD is useful in the management of patients with typical symptoms of GERD without alarm features (dysphagia, odynophagia, weight loss, bleeding, or anaemia) [133].

Moreover, endoscopy is generally not considered necessary for evaluating patients with suspected extra-esophageal manifestations of GERD with symptoms such as choking, coughing, hoarseness, asthma, chronic sore throat or dental erosions, because most of these patients will not present endoscopic evidence of erosive esophagitis, especially when taking empiric medical therapy for GERD [136]. A recent study by Krause et al. analyzed 756 patients with chronic laryngeal symptoms, observing endoscopic findings in 47 % of cases, including esophagitis (17 %) and hiatal hernia (37 %). The study found that mild to moderate erosive reflux disease correlated with objective GERD on ambulatory monitoring. These results suggest that esophagogastroduodenoscopy (EGD) may be beneficial for evaluating laryngopharyngeal reflux (LPR), even in the absence of typical GERD symptoms [137].

To optimize the diagnostic accuracy for GERD and evaluate for erosive esophagitis (EE), it is essential to perform diagnostic endoscopy after discontinuing PPIs for at least 2 weeks, and ideally up to 4 weeks if feasible. A small prospective study assessing relapse of EE in patients with Los Angeles (LA) grade C EE who healed under PPI therapy, drug discontinuation resulted in EE relapse in as little as one week [138]. When endoscopy reveals severe esophagitis (LA grade C, D), a twice-daily PPI regimen for 8 weeks and repeating endoscopic assessment after PPI therapy for 8–12 weeks is recommended to ensure healing of EE and to rule out the presence of underlying BE [139].

Statement 1.12: The Panel recommends AGAINST routine mucosal sampling of the esophagus or gastro-esophageal junction in patients with heartburn and/or other symptoms suggestive for uncomplicated GERD and normal findings on endoscopy.
Statement endorsed, overall agreement: 86.96 %%: *A* + 47.83, A 39.13, A- 0 %, D- 8.69 %, D 4.35, *D* + 0 %.
LE: Strong recommendation, moderate level of evidence.

Summary of evidence: When esophagitis is endoscopically evaluated, esophageal mucosal biopsies should be collected only in case of: immune-compromised state of the patient; proximal distribution of esophagitis; presence of irregular or deep ulceration; presence of esophageal mass or mucosal nodularity; presence of

irregular or malignant-appearing esophageal stricture; bullous lesions suggestive for esophageal pemphigus vulgaris; pictures suggestive for EoE (rings, linear furrows, white plaques, edema, strictures, crepe paper eosphagus, fragile mucosa); reporting of dysphagia and/or bolus impaction, particularly in young males with atopy. In these clinical conditions, biopsies (histological or cytological) are needed to exclude other diagnoses [134]. Moreover, microscopic esophagitis assessment could be useful in inconclusive diagnoses of GERD in order to refute or confirm the diagnosis of GERD, as suggested by the Lyon Consensus [134].

However, although microscopic esophagitis is frequent in patients with GERD symptoms, even when mucosal lesions are not visible, limited data is available to suggest that histological alterations are useful to guide therapy [140]. In case of endoscopic detection of EE, 8 weeks of PPI treatment is required to achieve mucosal healing, since the presence of active inflammation can compromise the histological diagnosis of concomitant BE and dysplasia [141,142]. Indeed, upon healing of EE, BE can be identified in up to 12 % of cases. In these cases, it might be correct to repeat endoscopy, particularly if moderate to severe esophagitis (LA grade B, C and D) is present, and to perform endoscopic biopsies to detect BE or BE-associated dysplasia [133].

In conclusion, endoscopic biopsies are mainly recommended to obtain histologic confirmation of endoscopically suspected BE or identify patients with EoE [18]. Otherwise, routine endoscopic biopsies are not recommended.

Statement 1.13: The Panel recommends FOR performing oesophageal manometry to appropriately locate the lower oesophageal sphincter and, therefore, correctly positioning pH or pH-impedance catheters.
Statement endorsed, overall agreement: 91.30 %: *A* + 78.26 %, A 13.04 %, A- 8.70 %, D- 0 %, D 0 %, *D* + 0 %.
LE: Strong recommendation, moderate level of evidence.
Statement 1.14: The Panel recommends FOR performing oesophageal manometry to evaluate oesophageal peristaltic performance prior to any anti-reflux endoscopic or surgical procedure.
Statement endorsed, overall agreement: 91.30 %: *A* + 78.26 %, A 13.04 %, A- 8.70 %, D- 0 %, D 0 %, *D* + 0 %.
LE: Conditional recommendation, low level of evidence.
Statement 1.15: The Panel recommends FOR oesophageal manometry combined with impedance in patients with suspected diagnosis of rumination syndrome and supragastric belching.
Statement endorsed, overall agreement: 91.30 %: *A* + 78.26 %, A 13.04 %, A- 8.70 %, D- 0 %, D 0 %, *D* + 0 %.
LE: Strong recommendation, moderate level of evidence.

Summary of evidence: Esophageal manometry is commonly performed to appropriately locate the lower oesophageal sphincter (LES) and, therefore, correctly positioning pH or pH-impedance catheters [143]. However, although not universally accepted [144], pH step-up could be used to correctly positioning the pH probe for reflux monitoring [145,146]. This method can be inaccurate in patients with large hiatal hernia or with disease-related or drug-induced changes in intragastric pH. However, considering that gastric impedance (which is not affected by pH) is significantly lower than esophageal impedance, Penagini and coworkers recently developed a rapid impedance step-up method that identifies the LES with good accuracy [147].

Moreover, high resolution manometry (HRM) findings may be helpful in corroborating the diagnosis of GERD in patients with inconclusive findings. Fragmented and failed swallows on HRM are associate with abnormal reflux burden [148,149]. Increasing spatial separation between LES and crural diaphragm is associated with significant increase in reflux and predicts an abnormal pH-impedance monitoring in GERD patients [31]. Disruption of the EGJ and absent contractility on HRM are both associated with lower impedance baseline values, a marker of impaired mucosal integrity and, therefore, of GERD [150]. Finally, a recently introduced score, namely the Milan score, calculated combining the assessment of ineffective esophageal motility (IEM), esophago-gastric junction contractile integral (EGJ-CI), evaluating esophagogastric junction (EGJ) type and straight leg raise (SLR) manoeuvre response has been developed and validated as a useful screening tool to stratify the risk and the severity of GERD, allowing a more comprehensive pathophysiologic assessment of the anti-reflux barrier. Esophageal manometry is also helpful to evaluate esophageal peristaltic performance prior to anti-reflux surgery [151].

It is widely accepted that patients presenting with severe esophageal dysmotility, including absent contractility, should not be treated with anti-reflux surgery. However, it has been shown that, one year after surgery, 95 % of patients with normal motility and 91 % of patients with non-severe ineffective esophageal motility (IEM) achieve a satisfactory outcome [152]. It has also been reported that HRM with multiple rapid swallowing test is helpful in predicting dysphagia occurrence in GERD patients undergoing anti-reflux surgery [153].

HRM may provide important findings in the evaluation of PPI non-responder patients. Intact EGJ metrics on HRM, together with normal reflux burden, predict non-response to PPI therapy [154]. Among patients with persisting esophageal symptoms despite optimal acid suppression, approximately 30 % have other diagnoses, including major esophageal motor disorders, rumination syndrome, and achalasia [155]. HRM can offer objective diagnosis of rumination syndrome and supragastric belching, and better differentiate these conditions from GERD [156].

Statement 1.16: The Panel recommends FOR pH or impedance-pH monitoring in patients with reflux-like symptoms not responding to medical treatments, in patients with extra-esophageal symptoms, prior to anti-reflux endoscopic or surgical procedures, in patients with belching disorders and to diagnose functional heartburn and reflux hypersensitivity in patients not responding to medical treatment.
Statement endorsed, overall agreement: 100 %: *A* + 73.91 %, A 26.09 %, A- 0 %, D- 0 %, D 0 %, *D* + 0 %.
LE: Strong recommendation, moderate level of evidence.

Summary of evidence: pH-impedance monitoring, a more accurate diagnostic tool than traditional pH-metry, is currently considered as the most accurate method the gold standard to detect and characterize gastro-oesophageal reflux episodes [157]. Wireless pH monitoring is indicated in case of intolerance of the transnasal catheter [158]. A prolonged wireless pH monitoring beyond 24 h is able to increase sensitivity of reflux detection and symptom reflux association indexes [158].

Ambulatory reflux monitoring is indicated in patients with unproven GERD (i.e. no prior evidence of conclusive reflux disease) and with reflux-like symptoms (heartburn, regurgitation and non-cardiac chest pain) unresponsive to empirical PPI therapy [159,160]. Also, patients with extra-esophageal symptoms (chronic cough or laryngeal symptoms) should be investigated with pH-impedance monitoring as first-line test. Indeed, it has been shown that chronic cough can be associated with weakly acidic reflux, thus recommending the use of pH-impedance monitoring rather than pH test alone in these patients to diagnose functional heartburn or reflux hypersensitivity [161,162]. GERD testing is also recommended before or after any anti-reflux endoscopic or surgical procdure. It has been shown that abnormally high total number of reflux episodes detected by pH-impedance monitoring performed

off therapy predicts a good surgical outcome if supragastric belching and rumination syndrome have been ruled out [163]. Furthermore, it has been demonstrated that abnormal pH values and presence of typical symptoms seem to better predict a positive outcome after anti-reflux surgery [164]. Furthermore, there is growing evidence that bariatric surgery can negatively impact esophageal function, potentially leading to the development or exacerbation of motility disorders and GERD [165–171]. As a result, recent international guidelines have been published addressing this important issue [172].

An important decision prior to ambulatory reflux monitoring is whether to test while on or off PPI therapy. If GERD is not yet proven, testing should be performed off PPI in order to document if abnormal reflux metrics are present. In patients with previous diagnosis of GERD (LA grade B, C and D erosive esophagitis, BE and refractory peptic stricture), testing should be performed while on therapy, in order to demonstrate if PPI failure is associated with residual acid burden and/or the association between symptoms and weakly acidic refluxes [160]. pH-impedance monitoring is considered the most appropriate test for the evaluation of patients with abnormal belching [173].

In addition to pH-impedance monitoring, high-resolution manometry (HRM) of the esophagus is extremely useful before anti-reflux surgery. Evaluating esophageal motility with HRM is essential to exclude motor disorders, such as achalasia, that are not amenable to anti-reflux surgery. If esophagogastric junction outflow obstruction (EGJOO) is present, it must be addressed prior to surgery. Anti-reflux surgery should be approached with caution in patients with distal esophageal spasm or a hypercontractile esophagus. Additionally, assessing the presence and severity of a hiatal hernia—measured by lower esophageal sphincter–crural diaphragm (LES-CD) separation—is crucial before proceeding with any anti-reflux procedure. This topic, along with post-surgical functional evaluation, is thoroughly discussed in the Padova Consensus [174]. Supplementary Table 2 summarises the normal values for esophageal pH-impedance monitoring [175,176].

Statement 1.17: The Panel recommends AGAINST barium esophagram to diagnose GERD.
Statement endorsed, overall agreement: 91.30 %: *A* + 78.26 %, A 13.04 %, A- 4.35 %, D- 4.35 %, D 0 %, *D* + 0 %.
LE: Strong Recommendation, moderate level of evidence.

Summary of evidence: Barium swallow allows to assess the characteristic of esophago-gastric junction (EGJ) and its dynamic nature to a possible risk factor of GERD [177]. This test enables to evaluate GERD-related complications such as esophagitis, peptic strictures or esophageal adenocarcinoma [178–180]. On radiography it is possible to detect finely nodular or granular appearance with poorly defined radiolucencies due to mucosal edema and inflammation, flat ulcers and erosions in the distal esophagus, thickened longitudinal folds as a result of submucosal inflammation, circumferential stricture and protruded lesion in the distal esophagus [178–180]. Double-contrast esophagram has a major sensitivity than single-contrast study to reveal reflux esophagitis when mucosal abnormalities are represented by granular pattern and erosions [178–180]. Therefore, the use of the combined examination technique is recommended [178].

On the other hand, although these findings have been associated with GERD, it is difficult to recognize the correct aetiology of the different lesions encountered at the esophagograms and it is usually necessary to perform an upper endoscopy with biopsies or reflux monitoring to obtain a definitive diagnosis [180]. Furthermore, it is important to remember that NERD is the most frequent phenotype of GERD and in this condition barium radiograms is not useful. As further confirmation, Saleh et al., even if in a limited sample of study population, have demonstrated that a presence or absence of GERD during barium esophagogram does not correlate with objective evidence of GERD at 24-h pH-impedance monitoring [79,181–183].

SECTION 2. Treatment (Fig. 1 and Fig. 2, Table 2)
Statement 2.1: The Panel recommends FOR offering lifestyle advices (healthy eating, weight reduction in overweight and obese subjects, smoking cessation, avoidance of "trigger foods", avoiding meals within 2–3 h before bedtime) for GERD symptom control. Head of the bed elevation and nocturnal left lateral decubitus position may help some patients.
Statement endorsed, overall agreement: 86.96 %: *A* + 65.22 %, A 21.74 %, A- 8.70 %, D- 4.35 %, D 0 %, *D* + 0 %.
LE: Conditional recommendation, low level of evidence.

Summary of evidence: Lifestyle and diet advice are widely used in the non-pharmacological management of patients with GERD, based on the possible influence of dietary habits and food ingestion on LES pressure and gastric emptying rate [184]. However, supporting data for these recommendations are limited and contradictory, often deriving from small and uncontrolled studies, with a great heterogeneity due to the different dietary habits of the study populations, which also influenced the quality of systematic reviews and meta-analyses [185].

A 2014 systematic review by NICE found some evidence suggesting that obesity has a weak role in GERD but there is little support for other lifestyle measures [184].

According to this review, physical exercise >30 min >3 times/week) was negatively correlated with GERD (OR=0.7, 95 % CI 0.6–0.9) whereas smoking (OR=1.19, 95 % CI 1.12–1.264) and alcohol consumption (OR=1.278, 95 % CI 1.207–1.353) were positively correlated with GERD [184].

Weight loss has been proved to be effective in reducing symptoms and PPI use and dosage in GERD patients [186,187]. Emerging data indicates that healthy diets involving high intakes of vegetable proteins, fruits, and whole grains, such as the Mediterranean diet, reduce the risk of GERD and postprandial GERD symptoms [188,189].

Two systematic reviews have been published more recently. A review of 72 studies found that GERD was associated with midnight snacking (OR=5.08, 95 % CI 4.03–6.4), skipping breakfast (OR=2.7, 95 % CI 2.17–3.35), eating quickly (OR=4.06, 95 % CI 3.11–5.29), consuming very hot foods (OR=1.81, 95 % CI 1.37–2.4), eating within 3 h before bedtime (OR=7.45, 95 % CI 3.38–16.4)) and high-fat diet (OR=7.57, 95 % CI 4.56–8.91). In contrast, a vegetarian diet (OR=0.34, 95 % CI 0.21–0.55) was negatively associated with GERD [190]. A second systematic review, which included 25 studies, found an association between some triggering foods (high-fat, spicy, fried, citrus foods, carbonated beverages, and tea) and the risk of GERD. In contrast, smoky foods, salty foods, coffee, alcohol, chocolate, and dairies did not appear to contribute to the risk of GERD [191].

Additionally, a prospective study carried out in primary care in 100 patients with reflux symptoms showed that 85 % of patients can identify at least one symptom-triggering food (most spicy foods, chocolate, pizza, tomato, fried foods). The study also found that abstention from these foods led to a reduction in symptom score by >25 % at a short-term follow-up of two weeks [192].

In 2021, the results of two large observational studies were published. The Nurses's Health Study II, which included 42,955 women and 392,215 person-years of follow up, found that never smoking, prudent diet, daily physical activity, being with normal BMI and daily intake of coffee/soda/tea were independently associated with reduced risk of GERD symptoms on initiation of PPI treatment (OR=0.47; 95 % CI 0.41–0.54 for those with 5 anti-

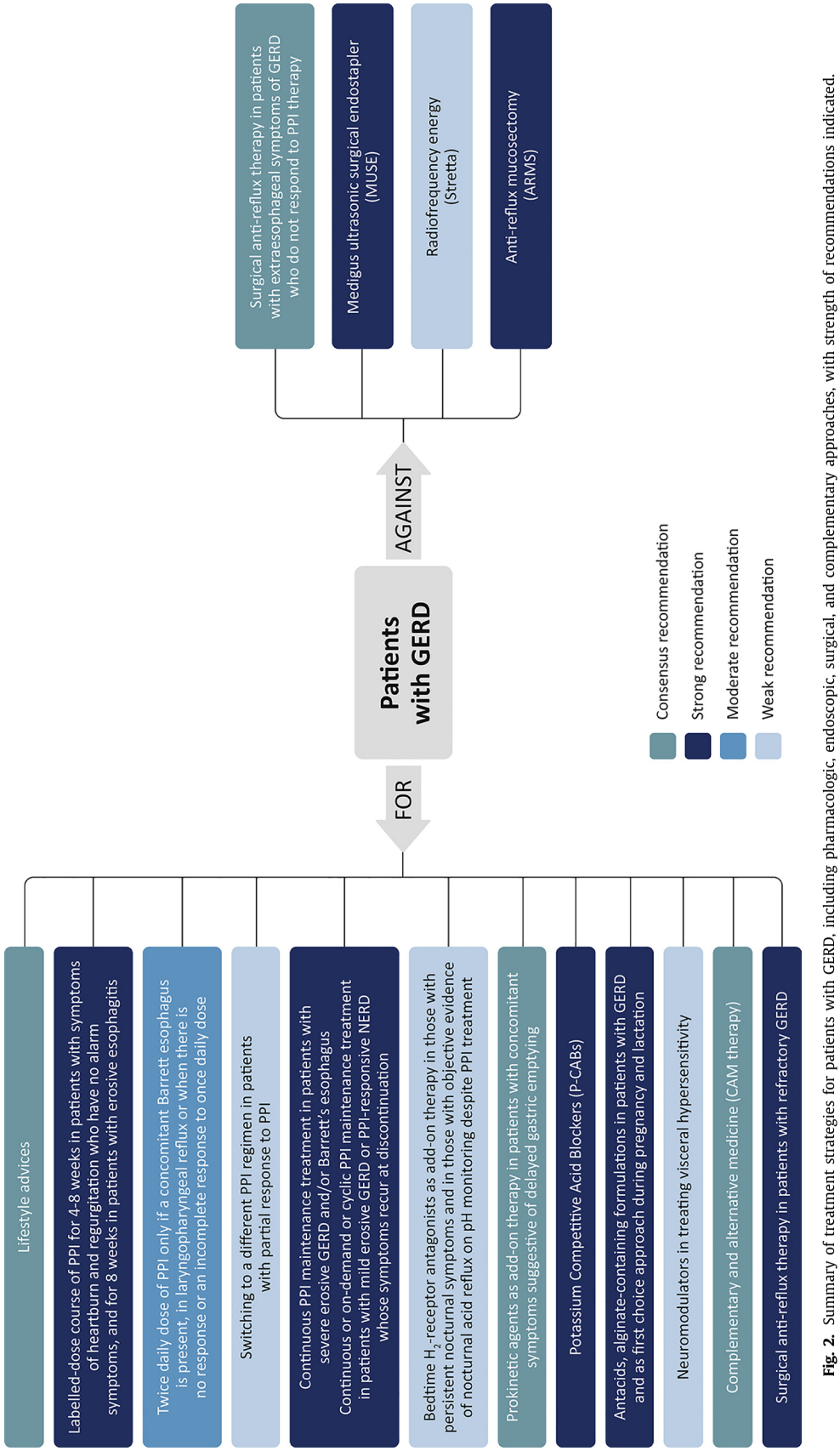

Fig. 2. Summary of treatment strategies for patients with GERD, including pharmacologic, endoscopic, surgical, and complementary approaches, with strength of recommendations indicated.

reflux lifestyle factors [193]. In addition, the Melbourne Collaborative Cohort study, involving 20,926 participants, showed that in men total fat intake was slightly associated with increased risk of GERD (OR=1.5 95 % CI 1.01–1.09), whereas total carbohydrate intake (OR=0.89, 95 %CI 0.82–0.98) and starch intake (OR=0.94, 95 % CI 0.75–0.94) were associated with reduced risk [194].

A recent systematic review (including 5 studies and 228 patients) evaluated the effect of head of bed elevation to relieve GERD symptoms. While definitive recommendations could not be made, a high-quality crossover trial demonstrated a clinical important reduction in symptom scores at 6 weeks (OR: 2.1; 95 % CI 1.2 to 3.6) [195]. Additionally, the left lateral decubitus position was associated with significantly shorter nocturnal esophageal acid exposure time and faster esophageal acid clearance compared to both supine and right lateral decubitus positions [196].

In conclusion, individual patients may benefit from lifestyle modifications and, since these changes may also provide additional health benefits, such interventions are certainly advisable.

Statement 2.2: The Panel recommends FOR a labelled-dose course of PPIs for 4–8 weeks, once daily before breakfast, in patients with symptoms of heartburn and regurgitation who have no alarm symptoms, and for 8-week in patients with erosive esophagitis
Statement endorsed, overall agreement: 91.30 %: *A* + 69.56 %, A 21.74 %, A- 4.35 %, D- 4.35 %, D 0 %, *D* + 0 %.
LE: Strong recommendation, moderate level of evidence.
Statement 2.3: The Panel recommends FOR a labelled-dose course of PPIs for 8–12 weeks in patients who have extra-esophageal and concomitant typical GERD symptoms.
Statement endorsed, overall agreement: 91.30 %: *A* + 69.56 %, A 21.74 %, A- 4.35 %, D- 4.35 %, D 0 %, *D* + 0 %.
LE: Conditional recommendation, low level of evidence.

Summary of evidence: In GERD patients who are unsatisfied with lifestyle interventions and over-the-counter therapies, PPIs represent the most effective medications, owing to their potent and long-lasting acid suppression. Treatments that do not act on gastric acid inhibition, such as alginates, have shown to be effective on GERD symptoms when compared with placebo or antacids (OR = 4.42, 95 % CI 2.45–7.97, $P < 0.01$), but they are less effective than PPIs or H_2RAs (OR = 0.58, 95 % CI 0.27–1.22, $P < 0.01$) [197]. A recent systematic review with network meta-analysis, including RCTs involving 10,735 subjects with endoscopy-negative reflux disease, confirmed these findings. The analysis assessed the ability of different treatments to achieve complete relief of symptoms. For relief of symptoms between ≥2 and <4 weeks, omeprazole 20 mg o.d. (P-score 0.94) ranked first, followed by esomeprazole 20 mg o.d. or 40 mg o.d., which ranked second and third, respectively. For to achieve complete relief at 4 weeks or more, dexlansoprazole 30 mg o.d. (P-score 0.95) ranked first. The second and third positions were occupied by a combination of 30 ml alginate q.i.d. with omeprazole 20 mg o.d., and 30 ml alginate t.i.d. All drugs were found to be safe and well-tolerated [103].

A Cochrane review found that PPIs and H_2RAs were more effective than placebo for heartburn relief in the short-term treatment of patients with uninvestigated heartburn (OR for PPIs: 0.37, 95 % CI 0.32 to 0.44) and NERD (OR for PPI: 0.71, 95 % CI 0.65 to 0.78). In addition, PPIs were more effective than H_2RAs in controlling GERD symptoms both in univestigated patients (RR = 0.66, 95 % CI 0.60–0.73, $P < 0.01$) and in patients with NERD (RR = 0.78,95 % CI 0.62–0.97, $P = 0.03$) [198].

Overall, heartburn remission rates with PPIs vary based on the condition being treated [190]:

- **Erosive Esophagitis (EE):** 56 % to 77 % of patients achieved heartburn remission (placebo response: 7.5 %).
- **Uninvestigated Heartburn:** 37 % to 61 % of patients experienced heartburn relief (placebo response: 25.1 %).
- **Non-Erosive Reflux Disease (NERD):** 37 % to 61 % of patients experienced relief (placebo response: 12.6 %).

Healing of esophagitis occured in 72 % –83 % patients with erosive disease (placebo response: 28.3 %).

The lower response rate in NERD can be attributed to the heterogeneity of this group of patients, which included subjects with weakly acidic reflux or functional heartburn, whose symptoms arise from factors other than increased or normal esophageal acid exposure [199–201].

An original Markov health economic model demonstrated that 8 weeks of treatment for healing severe esophagitis was more cost-effective than 4 weeks of treatment [184]. In addition, PPIs have shown high efficacy also in patients with reflux-induced chest pain. A meta-analysis of 6 RCTs, involving patients who underwent 24-hour esophageal pH recording, found that 56 %–85 % of reflux-positive patients benefitted from PPI treatment, compared with 0 %–17 % of reflux-negative patients [202].

A meta-analysis including 10 studies (15,316 patients) found that there is little difference in GERD symptom relief and healing rates among the various PPIs [203]. Another meta-analysis assessed the relative potencies of standard-dose PPIs, estimating their omeprazole equivalents (OEs) as follows: pantoprazole (0.23 OEs), lansoprazole (0.90 OEs), omeprazole (1.00 OEs), esomeprazole (1.60 OEs), and rabeprazole (1.82 OEs) [204]. These potency differences may influence PPI selection in clinical practice, particularly for patients requiring stronger acid suppression. For instance, esomeprazole and rabeprazole may be preferred in cases of severe GERD or *Helicobacter pylori* eradication therapy, where more potent acid suppression is beneficial [205,206].

It is worth mentioning that PPIs work by irreversibly inhibiting the activated H^+, K^+-ATPase proton pump in the gastric parietal cells and their effect lasts until new proton pumps are generated. Since meals stimulate proton pump activity, PPIs should be taken daily, 30 – 60 min before a meal (usually breakfast or/and dinner) to achieve the best antisecretory effect.

Management of extra-esophageal symptoms of GERD remains challenging due to the potential heterogeneity of the underlying pathophysiological mechanisms in these patients. Clinical outcomes, treatment regimens, and treatment duration vary across studies. However, PPI therapy has shown to be effective, especially when typical symptoms are present alongside extra-esophageal symptoms [5]. The dosage and treatment durations used in clinical trials for extra-esophageal symptoms often differ from the standard recommendations, meaning that they are not always approved by regulatory authorities. One systematic review on the role of PPIs in asthma found a small improvement in morning peak expiratory flow, but this improvement was unlikely to be clinically significant [207].

A systematic review suggests that acid suppressing drugs are more beneficial in patients with chronic cough and pathologic esophageal acid exposure (range, 12.5 %−35.8 %) compared to those without (range, 0.0 %−8.6 %) [208]. The efficacy of PPIs in treating LPR remains unclear. A meta-analysis of 8 studies showed no significant difference in overall improvement between PPI and placebo groups (RR = 1.22, 95 % CI0.93–1.58, $P = 0.149$) [209]. However, a more recent one (including 10 RCTs) reported a pooled RR of 1.31, suggesting a small improvement with PPI treatment [210]. Conversely, another meta-analysis found no advantage of PPI therapy over placebo in improving of the reflux finding score (SMD=0.62; 95 % CI, −0.96–2.19) [211].

Statement 2.4: The Panel recommends FOR twice daily dose of PPIs in patients with GERD only if a concomitant Barrett esophagus is present, in proven laryngo-pharyngeal reflux or when

there is no response or an incomplete response to once daily dose.
Statement endorsed, overall agreement: 91.30 %: *A* + 52.17 %, A 39.13 %, A- 4.35 %, D- 4.35 %, D 0 %, *D* + 0 %.
LE: Moderate Recommendation, low level of evidence.

Summary of evidence: The use of high-dose of PPI has increased over the time, not only in GERD patients [212,213]. Currently, twice daily dose PPIs is approved by U.S. Food and Drug Administration (FDA) only in patients with pathological hypersecretory conditions (such as Zollinger-Ellison syndrome) or – in combination with antimicrobials – for the eradication of *H. pylori* infection [212,214].

In a RCT, Chen et al. demonstrated that higher doses of oral PPIs can prevent re-bleeding from peptic ulcer disease in acute phase. However, there is limited evidence to support their use in patients with healed esophagitis or for preventing peptic ulcer complications [212,215]. In clinical practice, twice daily PPI dosing is often used empirically in patients who have not responded or have had an inadequate response to once daily PPI dosing. This holds true also for patients with chest pain (after exclusion of cardiac aetiology) and those with pharyngo-laryngeal reflux disease [216]. It is worthwhile mentioning that a lack of response to twice-daily dosing may prompt further endoscopic or pathophysiological examination [216]. However, most efficacy data for PPI therapy come from studies using once-daily dosing [216]. Current ACG Clinical Guideline and American Gastroenterological Association Medical Position Statement on the management of GERD recommend high-dose PPIs in patients with suspected laryngo-pharyngeal reflux or Barrett's oesophagus, even though no study specifically demonstrates their superiority to standard-dose to prevent extension or progression to dysplasia or cancer [212,216,139]. Furthermore, PPIs at any dose are ineffective in managing laryngo-pharyngeal symptoms [217]. Finally, in a trial of 117 GERD patients with typical symptoms using higher doses of PPIs, a progressive PPI dose reduction to standard dose (single-dose therapy) did not lead to recurrence of symptoms in 80 % of patients [218].

Statement 2.5: **The Panel recommends FOR switching to a different PPI regimen in patients with partial response to PPI treatment to improve symptom control.**
Statement endorsed, overall agreement: 84.70 %%: *A* + 50 %, A 34.70 %, A- 3.80 %, D- 3.80 %, D 7.70 %, *D* + 0 %
LE: Weak Recommendation, low level of evidence

Summary of evidence: GERD symptoms may persist in up to 60 % of patients taking PPIs in the primary care setting and 44 % of them in secondary care [219,220]. For those with persistent GERD symptoms despite PPI treatment, switching to a different PPI or adjusting the PPI regimen may help improving symptoms. In a RCT involving 328 patients who had persistent GERD symptoms despite a 30-day trial of lansoprazole 30 mg once daily, switching to esomeprazole 40 mg once daily was at least as effective as lansoprazole 30 mg twice daily for increasing the percentage of heartburn-free days (54.4 % vs 57.5 %, respectively) after eight weeks [221]. Another RCT showed improvement of persistent GERD symptoms when switching from lansoprazole 30 mg once daily to omeprazole 40 mg once daily [222]. In a RCT, conducted in the primary care setting, 1564 patients with persistent GERD symptoms while on antisecretory therapy were studied. Of these, 973 were switched to esomeprazole 40 mg (94.4 %) or 20 mg (5.6 %) once daily and 591 controls were continued on their original medication (non-esomeprazole PPI the majority). After four weeks, there was a statistically significant improvement in global overall symptom score in the esomeprazole arm (58 % vs 29 %; $p < 0.0001$) [223]. In a multicentre observational study including 4929 patients treated for GERD with PPIs other than esomeprazole, those switched to esomeprazole (mostly 40 mg) showed significant improvement. Prior to switching, 21.9 % of patients were satisfied with treatment and 84.0 % had reflux symptoms. After switching, 88.0 % of patients were satisfied and only 26.9 % reported persistent symptoms [224]. Finally, in a multicentre prospective study, 32 patients with erosive esophagitis with persistent GERD symptoms despite at least of 8-week treatment with omeprazole, lansoprazole, or rabeprazole (standard or high dose), were switched to esomeprazole 20 mg once daily. At week 4, 57.6 % of patients reported improvement of heartburn and 46.4 % had improved acid regurgitation compared to baseline [225].

Thus, the available evidence suggests that switching to a different PPI or adjusting PPI regimen may be beneficial for controlling symptom in patients with persistent GERD symptoms. However, since PPI metabolism and response may be affected by cytochrome P450 2C19 (CYP2C19) polymorphism [226], switching to PPIs whose bioavailability is less affected by CYP2C19 metabolism (e.g., esomeprazole, pantoprazole or rabeprazole) might be preferable [227,228]. In particular, esomeprazole, together with its metabolite (esomeprazole sulfone), is a powerful inhibitor of CYP2C19 and does inhibit its own metabolism, rendering all subjects "slow metabolizers" [229]. This will lead to more consistent acid suppression. In addition, esomeprazole achieves the highest intragastric pH and has the longest duration of antisecretory activity among available PPIs,

Statement 2.6: The Panel recommends FOR continuous PPI maintenance treatment in patients with severe erosive GERD and/or Barrett's esophagus.
Statement endorsed, overall agreement: 95.65 %%: *A* + 73.91 %, A 21.74 %, A- 0 %, D- 0 %, D 4.35 %, *D* + 0 %.
LE: Strong Recommendation, moderate level of evidence.
Statement 2.7: The Panel recommends FOR Continuous or cyclic PPI or on-demand maintenance treatment in patients with mild erosive GERD or PPI-responsive NERD whose symptoms recur at discontinuation.
Statement endorsed, overall agreement: 95.65 %%: *A* + 73.91 %, A 21.74 %, A- 0 %, D- 0 %, D 4.35 %, *D* + 0 %.
LE: Strong Recommendation, moderate level of evidence.

Summary of evidence: EE and GERD symptoms rapidly recur after treatment discontinuation in most patients, making continuous treatment necessary to maintain mucosal healing and symptom control [230]. However, a recent clinical trial found that - among patients with reflux symptoms who stopped taking PPIs - those with abnormal acid exposure time on prolonged esophageal pH monitoring were less likely to discontinue treatment [231].

A meta-analysis of patients with EE showed that continuous PPI maintenance treatment was significantly more effective than placebo for maintaining endoscopic remission over a six-month follow-up (82.4 % vs 10.6 %, respectively) [232]. Notably, continuous treatment was significantly more effective than on-demand PPI treatment in patients with severe EE (LA grade C-D) [233].

EE is independently linked to subsequent development of BE, a precursor of esophageal adenocarcinoma (EAC) [234,235]. In this context, another meta-analysis found that continuous PPI maintenance treatment reduced the risk of EAC and/or high-grade dysplasia (HGD) in patients with BE [236]. Specifically, PPI use was associated with a 71 % reduction in risk of EAC and/or BE-HGD in patients with BE (adjusted odds ratio [aOR] 0.29, 95 % confidence interval [CI] 0.12–0.79). Long-term PPI use (>2–3 years) provided a greater protective effect against HGD/EAC (aOR 0.45; 95 % CI 0.19 to 1.06), while short-term use (<2–3 years) did not [236]. Similar findings were reported in another recent meta-analysis, where PPI use was linked to a reduced risk of BE progression to HGD or EAC (OR 0.47, 95 % CI 0.32–0.71, $p < 0.001$) [237]. In the duration-

response analysis, there was a linear inverse relationship between duration of PPI use and HGD/EAC risk, with a 19 %, 35 %, and 48 % reduction in risk after 12, 24, and 36 months of PPI use, respectively.

Up to 75 % of patients with NERD experience symptoms recurrence when treatment is discontinued, indicating that maintenance treatment may be necessary for patients with PPI-responsive NERD [238]. A recent meta-analysis of RCTs found that taking PPIs on ~~an~~ as needed basis was as effective as continuous treatment in terms of treatment failure and satisfaction in patients with mild EE and NERD. Continuous treatment was slightly effective for symptom relief (risk ratio [RR] 1.09; 95 % CI, 1.01–1.18), though the on-demand group took half the number of the pills compared to the continuous treatment group [233]. Along the same lines, in another meta-analysis the on-demand strategy allowed a significant reduction of the number of pills used, but was associated with an increased the risk of 'lack of symptom control' compared with continuous treatment (RR 1.71, 95 % CI 1.31–2.21) [239]. However, the on-demand PPI strategy was associated with higher adherence to treatment and greater patient satisfaction compared to continuous PPI treatment in mild EE and NERD [240].

The American Gastroenterological Association (AGA) has provided guidance on the management of long-term PPI therapy [241]. According to the AGA, routine supplementation with calcium, vitamin D, or other vitamins does not conclusively reduce fracture risk, nor is routine bone mineral density testing or monitoring of vitamin or mineral levels recommended for long-term PPI users [241] However, ensuring that patients meet the recommended dietary allowances for these nutrients is reasonable, particularly if their intake is insufficient [241]

A systematic review [242] indicates that long-term PPI therapy induces moderate hypergastrinemia in most individuals, with a significant increase in serum chromogranin A (CgA) levels observed even after short-term treatment. [243] The prevalence of enterochromaffin-like (ECL) cell hyperplasia increases progressively with long-term PPI use; however, none of the patients in these studies developed neuroendocrine tumors (NETs) [242]. *H. pylori*-positive patients receiving long-term PPI therapy have a higher risk of developing corpus-predominant gastritis compared to *H. pylori*-negative patients [242]. Therefore, routine measurement of gastrin and CgA is not necessary for most patients on long-term PPIs but may be useful in selected cases.

Statement 2.8: The Panel recommends FOR the use of bedtime H_2-receptor antagonists in patients with GERD, particularly as *add-on* therapy, in those with persistent nocturnal symptoms and in those with objective evidence of nocturnal acid reflux on pH monitoring despite PPI treatment.
Statement endorsed, overall agreement: 86.96 %%: *A* + 39.13 %, A 47.83 %, A- 15.04 %, D- 0 %, D 0 %, *D* + 0 %.
LE: Weak recommendation, low level of evidence

Summary of evidence: H_2RAs, including ranitidine, famotidine, cimetidine and nizatidine, are competitive and reversible antagonists of H_2-receptors located on parietal cells. They inhibit histamine-induced acid secretion in a competitive manner, but they also affect the acid secretion triggered by other mediators such as acetylcholine and gastrin. Compared with PPIs, H_2RAs have a faster onset of action, but their antisecretory effect is less potent and shorter-lasting. Additionally, over time, tolerance to H2RAs can develop, which may reduce their clinical effectiveness [244].

In patients with EE, meta-analyses have shown that PPIs results in a significantly faster healing rate (12 % per week) compared to H_2RAs (6 % per week) and provide more complete heartburn relief (11.5 % per week for PPIs vs 6.4 % per week for H_2RAs). These findings support the use of PPIs as first-line treatment in these patients [245,246].

Similarly, for patients with NERD, a Cochrane systematic review found that PPI therapy was more effective than H_2RAs and prokinetics for heartburn relief. The RR for heartburn remission was 0.78, for PPIs vs H2Ras (95 % CI 0.62 to 0.97) and 0.72 for PPIs vs prokinetics (95 % CI 0.56 to 0.92). However, a step-down therapy approach (switching from more potent to less expensive medication) with H_2RAs can be considered as an acceptable option, particularly in patients with NERD [218]. Inadomi et al. demonstrated that more than half of patients who became asymptomatic on PPI therapy could successfully step down to less expensive medications while maintaining symptom control [218].

H_2RAs might also be a therapeutic option for patients with GERD who have an incomplete symptom relief on PPI therapy. In fact, in patients with persistent nocturnal symptoms and in those with objective evidence of nocturnal acid reflux on pH monitoring despite PPI treatment, adding a bedtime H_2RA should be considered [247–249]. As a matter of fact, in a retrospective cohort study, adding ranitidine 300 mg or famotidine 40 mg at night improved overall symptoms by 72 % and night-time symptoms by 74 %, although 13 % of patients discontinued the H_2RA after 1 month due to tachyphylaxis.[7] Moreover, A recent network meta-analysis, comparing all the antisecretory regimens found that - amongst the available treatments - the PPI/H_2RA combination exhibited the highest cumulative probability of controlling nocturnal acidity, an effect exceeded only by P-CABs (not yet marketed in Europe) [250].

There is limited evidence supporting the use of H_2RAs in patients intolerant or allergic to PPIs, although this approach seems logical [249].

Importantly, tachyphylaxis can develop within 10 days of starting H_2RA therapy, leading to drug discontinuation in up to 13 % of patients [251,252]. Therefore, H_2RAs would be better taken on demand or intermittently, whether as *add-on* therapy to a double PPI therapy or as a substitute for the second PPI dose [253].

Statement 2.9: **The Panel recommends FOR the use of prokinetic agents as add-on therapy for patients with GERD with concomitant symptoms suggestive of delayed gastric emptying.**
Statement endorsed, overall agreement: 84.70 %: *A* + 57.70 %, A 27 %, A- 11.50 %, D- 0 %, D 0 %, *D* + 3.80 %
LE: Conditional recommendation, moderate level of evidence

Summary of evidence Prokinetics are medications that increase LES pressure, enhance esophageal peristalsis, and accelerate gastric emptying. These include 5-hydroxytryptamine (5-HT) receptor agonists, dopamine receptor antagonists, muscarinic receptor agonist and cholinesterase inhibitors [254]. While prokinetics are approved for treating gastroparesis, they have also been suggested as an *add-on* therapy for some patients with refractory GERD, since delayed gastric emptying can contributed to symptom persistence [255].

An earlier meta-analysis found that combining prokinetics with PPIs in patients with GERD does not significantly improve symptom or endoscopic outcomes, and actually increases the risk of adverse events [254]. A more recent meta-analysis of 14 studies, however, showed that, compared to PPI monotherapy, adding prokinetics to PPIs did not elevate the rate of endoscopic responders (RR = 0.996, 95 % CI 0.929 – 1.068), but improved symptom response (RR = 1.185, 95 % CI 1.042 – 1.348) [256]. Moreover, in patients with refractory GERD, several RCTs have shown no improvement in reflux symptoms when 5-HT_4-receptor agonists, such as mosapride and reverexepride were added to PPI therapy in patients with refractory GERD [257–259].

Therefore, in patients without gastric emptying abnormalities, adding these drugs (even for a short period of time) should be carefully evaluated in terms of risk-benefit balance.

In addition, prucalopride, a full $5HT_4$-agonist, approved for treatment of constipation, has been shown to improve gastric emptying and reduce esophageal acid exposure in a randomized crossover study on healthy male subjects [173]. In a case report of 4 female patients with chronic constipation and PPI refractory GERD, 2 mg prucalopride daily reduced the number of acid and non-acid reflux episodes with simultaneous symptom improvement [260]. Although promising, these data are still insufficient to draw conclusions about the efficacy of prucalopride in GERD and to recommend its use in clinical practice.

In a double-blind RCT, the D_2-receptor antagonist domperidone administered (10 mg three times daily) combined with omeprazole 20 mg twice daily provided superior symptom relief compared to omeprazole alone. However, objective measures of GERD symptoms were identical between the two groups [261]. It's worth mentioning that long-term use (i.e., >12 weeks) of domperidone may be limited due to ~~side~~ adverse effects, such as insomnia, agitation and tardive dyskinesia [262].

Although evidence supporting the use of prokinetics as add-on therapy is limited, this approach is commonly used in clinical practice since *some* patients may experience symptom relief with prokinetics. Therefore, their use could be considered in patients with GERD presenting with symptoms suggestive of delayed gastric emptying and in those with an objective demonstration (by scintigraphy or breath test) of delayed emptying rate.

When using prokinetics, it is essential to carefully weigh the risks and benefits, taking their potential adverse effects into account [263,264]. Metoclopramide can cause central nervous system (CNS) adverse effects due to its ability to cross the blood-brain barrier. These effects include extrapyramidal symptoms (e.g., dystonia, parkinsonism, tardive dyskinesia), neuroleptic malignant syndrome, and serotonin syndrome, particularly when combined with serotonergic agents. Other reported side effects include drowsiness, fatigue, irritability, and restlessness. Additionally, metoclopramide may lead to endocrine disturbances such as hyperprolactinemia, which can result in galactorrhea, amenorrhea, gynecomastia, and impotence. Cardiovascular effects, including hypotension, hypertension, bradycardia, and fluid retention, have also been observed [263,264]. Domperidone, which crosses the blood-brain barrier to a lesser extent, is associated with fewer CNS side effects. However, it can prolong the QT interval, increasing the risk of serious arrhythmias. Other adverse effects include headache, abdominal pain, and diarrhea [263,264].

Due to these risks, the Italian Drug Agency (AIFA) does recommend limiting the use of metoclopramide and domperidone to no more than 5 and 7 days, respectively [265,266].

Statement 2.10: The Panel recommends FOR the use of baclofen for patients with refractory GERD. However, its use should be carefully considered and monitored due to the high rate of adverse effects.
Statement endorsed, overall agreement: 86.96 %: *A* + 30.44 %, A 56.52 %, A- 8.70 %, D- 4.35 %, D 0 %, *D* + 0 %.
LE: Moderate recommendation, moderate level of evidence.

Summary of evidence: A meta-analysis of 9 RCTs involving 883 patients with GERD and healthy controls found that baclofen, a gamma-amino butyric acid-B (GABA-B) agonist, reduced the number of reflux episodes, the average length of reflux episodes, and the incidence of transient lower oesophageal sphincter relaxations [267]. In a randomized, placebo-controlled trial comparing medical therapy (including baclofen) to anti-reflux surgery for PPI-refractory heartburn, blacofen showed no significant benefit over placebo after one year. However, the study was not adequately powered to detect a small, potentially significant effect for baclofen [268]. Another RCT by Ciccaglione et al. suggested that baclofen may be beneficial for regurgitation-predominant refractory symptoms and in belching [269]. In addition, baclofen was shown to be an effective treatment for patients with ruminant syndrome, likely due its effect on LES pressure [259].

A trial of baclofen (5–20 mg three times a day), starting with a low dose and gradually increasing based on clinical response, may be considered for patients with persistent symptomatic reflux despite optimal PPI therapy. It may also be useful for patients with regurgitation-predominant refractory symptoms, belching or ruminant syndrome. Two recent meta-analyses confirmed that baclofen - as an add-on treatment - can effectively improve the symptoms of patients with PPI-resistant GERD and improve DeMeester's score, leading however to an increased incidence of adverse effects [270,271].

In fact, the significant prevalence of adverse effects can limit its use in clinical practice. In fact, the most common reported ones are dizziness, somnolence, and constipation, with the higher incidence in long term use (up to 7.9 %, 20.9 %, 5.1 % respectively) [267,269].

Statement 2.11: The Panel recommends FOR the use of P-CABs as treatment of gastro-esophageal reflux disease.
Statement endorsed, overall agreement: 95.65 %%: *A* + 69.56 %, A 26.09 %, A- 4.35 %, D- 0 %, D 0 %, *D* + 0 %.
LE: Strong Recommendation, moderate level of evidence.

Summary of evidence: Potassium-competitive acid blockers (P-CABs) bind competitively and reversibly to the potassium-binding site of the H^+/K^+-ATPase[1]. These drugs display a better pharmacological profile than PPIs as they provide a more rapid onset of action, longer lasting acid suppression, and superior control of nocturnal acidity [272–274]. Four P-CABs (vonoprazan, tegoprazan, fexuprazan, and keverprazan) have been approved for erosive and non erose reflux disease. However, except for vonoprazan and tegoprazan, which are currently some South American markets, with vonoprazan being the only FDA-approved P-CAB – their availability is limited to some Asian Countries (Japan, Malaysia, Singapore, South Korea, Taiwan, and Thailand) [275].

A systematic review and meta-analysis comparing the efficacy and safety of vonoprazan versus PPIs included 6 RCTs, all conducted in Asia. The risk ratios (RR) for efficacy and adverse events between vonoprazan and PPIs were 1.06 (95 % CI: 0.99–1.13) and 1.08 (95 % CI: 0.96–1.22), respectively [276]. Subgroup analysis of patients with severe EE at baseline showed significantly better results for vonoprazan than lansoprazole, with an RR of 1.14 (95 % CI: 1.06–1.22) [269]. In addition, a recent network meta-analysis suggested that the healing effect of vonoprazan on EE is better than that of rabeprazole, but not superior to other PPIs [277]. The safety profile of vonoprazan is similar to that of PPIs.

In a recent RCT by Laine et al., adults with EE were randomized to receive vonoprazan 20 mg, or lansoprazole 30 mg, once-daily for up to 8 weeks. Patients who healed were re-randomized to vonoprazan 10 mg, vonoprazan 20 mg, or lansoprazole 15 mg, once-daily for 24 weeks. The study demonstrated that vonoprazan was both non-inferior and superior to lansoprazole in healing and maintaining healing of erosive esophagitis [278]. This benefit was most evident in patients severe erosive esophagitis (LA Grade C/D).

In a large RCT, involving 772 NERD patients, complaining heartburn for 4 or more days per week, subjects were randomized to placebo, vonoprazan 10 mg, or vonoprazan 20 mg. After 4 weeks, those on placebo were re-randomized to vonoprazan 10 mg or 20 mg, and those already on vonoprazan continued the same dose for 20 weeks [279]. Vonoprazan reduced heartburn, with the benefit starting as early as the first day of therapy. The effect persisted throughout the 20-week extension period, and there was no significant difference in efficacy between the 10 mg and the 20 mg

doses. A separate study by Fass et al. evaluated on-demand vonoprazan as a potential alternative to continued daily acid suppression therapy for the relief of episodic heartburn in NERD [280]. Overall, 458 patients with heartburn for ≥6 months and for ≥4/7 consecutive days received once-daily vonoprazan 20 mg during a 4-week run-in period. Results showed that 56.0 % of evaluable heartburn episodes in the vonoprazan 10 mg group and 60.6 % in the 20 mg met the criteria for complete and sustained relief compared to only 27.3 % in the placebo group ($p < 0.0001$). Additionally, vonoprazan provided complete symptom relief of heartburn episodes 1 h post-does, significantly more than placebo. On the basis of these results, vonoprazan was approved by FDA for the relief of heartburn associated with NERD

Tegoprazan has been approved for the treatment of EE and NERD in South Korea. A recent phase III demonstrated that tegoprazan was non inferior to esomeprazole 40 mg in terms of efficacy and safety for healing EE [281]. However, subgroup analysis for severe EE was not performed. In another RCT, tegoprazan showed superior efficacy compared with the placebo, along with a favorable safety profile, in patients with NERD [282]. A recent network meta-analysis, based on only three trials, found that tegoprazan 100 mg once daily was only slightly superior to placebo for achieving complete heartburn relief between ≥2 and <4 weeks of treatment in patients with NERD. All other results for P-CABs failed to reach statistical significance [103].

In summary, vonoprazan (at 2 weeks and 4 weeks) and tegoprazan (at 4 weeks) demonstrated non-inferiority to PPIs in terms of EE healing rates, with similar results at 8 weeks (pooled RR, 1.02; 95 % CI, 0.99–1.04) [283]. Available Asian and US/European data suggest that vonoprazan may be superior to PPIs in treating severe EE. The incidence of short-term adverse events was comparable between P-CABs and PPIs. Therefore, P-CABs are recommended as treatment of erosive reflux disease, particularly in the short term. A recent network meta-analysis suggested that the efficacy of vonoprazan in maintenance of healing of EE may ~~be~~ exceed that of some PPIs [284].

Asian and US/European placebo-controlled trials have shown an efficacy of P-CABs in NERD that appears to be comparable to that of PPIs. At the present time, P-CAB therapy for GERD is recommended by the South Korean and Chinese Consensus as well as by the Japanese Practice Guidelines and the Mexican Clinical Practice Recommendations [285–289].

Statement 2.12: The Panel recommends FOR the use of antacids and sucralfate as treatment of GERD symptoms.
Statement endorsed, overall agreement: 86.96 %%: *A* + 69.56 %, A 17.40 %, A- 8.70 %, D- 0 %, D 4.35 %, *D* + 0 %.
LE: Weak Recommendation, very low level of evidence

Summary of evidence: Antacids (aluminum-, calcium-, or magnesium-based compounds), act by neutralizing acid in the stomach, whereas sucralfate (a nonabsorbable, aluminum salt of sucrose orasulfate) creates a coating over the esophageal mucosa and gastric mucosa, exerting both site- and cyto-protective activities.

A systematic review with meta-analysis evaluating over-the-counter medications for GERD showed that both antacids (4 trials, treatment $n = 578$, placebo $n = 577$) and alginate/antacid combinations (4 trials, treatment $n = 146$, placebo $n = 138$) were more effective than placebo in providing symptom relief after 2 or 4 weeks of treatment [290]. Specifically, for antacids the absolute benefit increase over placebo was 8 % (95 % CI: 0–16 %, $P = 0.06$), with a relative benefit increase of 0.11 (95 % CI: 0.03–0.20) and a NNT of 13 (95 % CI: 6–250) [291–294]. For alginate/antacid combinations, the absolute benefit was 26 % (95 % CI: 12–41 %, $P < 0.0001$), while the relative benefit increase was 0.60 (95 % CI: 0.25–0.91) and the NNT only 4 (95 % CI: 2–9) [292,295–297].

Regarding sucralfate, its effectiveness as standalone therapy or as *add-on* medication was evaluated in various RCTs [246,298–300]. Simon et al. et al. found that sucralfate gel (b.i.d. for 6 weeks) was superior to placebo in patients with moderate to severe GERD symptoms but normal endoscopy, with a response rate of 71 % versus 29 % in the placebo group [298]. Herrera et al. showed that sucralfate suspension added to cimetidine improved daytime heartburn symptoms and overall endoscopic outcomes in patients with grade 2+ EE and abnormal pH-recording [299]. In addition, more patients exhibited endoscopic healing in the adjunctive sucralfate group than in the cimetidine-only group, without reaching however the statistical significance [299]. Donnellan et al. confirmed sucralfate's superiority over placebo for symptomatic relief. However, Khan et al. found no significant benefit in healing esophagitis when sucralfate was compared to placebo [300]. This was confirmed by a meta-analysis comparing the effectiveness of different medical treatments in the short-term management of reflux oesophagitis [246]. Taking into account the symptomatic benefit, the recent position statement on GERD management by the Indian Society of Gastroenterology suggested that patients with infrequent symptoms may be treated with antacids [301].

Statement 2.13: The Panel recommends FOR the use of alginate-containing formulations as treatment of GERD
Statement endorsed, overall agreement: 91.31 %: *A* + 86.96 %, A 4.35 %, A- 4.35 %, D- 0 %, D 4.35 %, *D* + 0 %.
LE: Strong Recommendation, moderate level of evidence.

Summary of evidence: Alginates are natural polysaccharides isolated from brown seaweed. Their ability to form viscous solutions and gels, coupled with their safety, have led to their use as pharmaceutical products. In particular, in the acid environment of the stomach, alginate reacts with intragastric acid to form a viscous raft floating over the gastric contents, acting a physical barrier to gastro-esophageal reflux [302]. They limit also the proximal migration of refluxed gastric contents and adhere to the esophageal mucosa, providing a protective effect due to mucoadhesion. Moreover, alginates-based compounds neutralise the 'acid pocket', a highly acidic area of the proximal stomach which develops postprandially and favours the occurrence of acid reflux episodes [303–305]. Two meta-analyses of RCTs on the efficacy of alginate-based compounds in GERD have been published so far [197,290]. In the study of Tran et al., alginate/antacid combinations were significantly better than a placebo in relieving GERD symptoms. The absolute benefit of alginates was 26 % higher than placebo, and the relative benefit was 0.60 [264]. In the larger (14 trials involving 2095 patients) and more recent analysis of Leiman et al., alginate treatments were found to be more effective than placebo or antacids in relieving GERD symptoms. However, when compared to PPIs or H_2RAs, alginates were less effective, though this difference was not statistically significant [197]. Therefore, alginates are more effective than placebo or antacids for treating GERD symptoms, with limited data suggesting that alginate may have similar clinical efficacy compared with PPIs [306].

There is conflicting evidence regarding the use of alginate as an *add-on* treatment for patients with GERD who have partial or no response to PPIs. Some studies have shown that alginate does not provide additional clinical benefits when added to PPI therapy. For instance, one study found no improvement in PPI-treated GERD patients when alginate was added compared to placebo [307]. Similarly, a recent RCT showed no significant benefit of combining alginate with PPIs versus using PPIs alone [308]. In contrast, other studies suggest that adding alginate may help reduce residual re-

flux symptoms in patients who still experience symptoms despite being on PPI therapy [309].

There are limited data on the effectiveness of alginate-based treatments for NERD, and more research is needed to determine its role in this population [306,310–312,103]. A recent network meta-analysis comparing the efficacy of PPIs, H_2RAs, P-CABs, and alginates, versus each other, or placebo, in patients with NERD, demonstrated that, in terms of achieving complete relief of symptoms between ≥2 and <4 weeks of treatment, 20 ml of alginate t.i.d. ranked fourth and performed similarly to omeprazole 20 mg o.d. and esomeprazole 20 mg or 40 mg o.d. [103] In addition, 30 ml of alginate q.i.d. combined with omeprazole 20 mg and 20 ml of alginate t.i.d. ranked second and third in terms of achieving complete relief of symptoms at ≥4 weeks of treatment [103].

However, these findings are based on only one small study, and further randomized controlled trials (RCTs) are needed to confirm the efficacy of alginate in NERD.

Based on the available evidence, alginate-containing formulations may be a useful adjunctive treatment for GERD, especially for patients with residual symptoms despite PPI therapy. However, the efficacy of alginate in different GERD phenotypes, particularly NERD, requires further investigation through larger, more robust studies.

Statement 2.14: The Panel recommends FOR the use of esophageal mucosal protectants as *add-on* treatment of GERD.
Statement endorsed, overall agreement: 82.61 %%: *A* + 60.87 %, A 21.74 %, A- 0 %, D- 0 %, D 4.35 %, *D* + 0 %.
LE: Weak Recommendation, low level of evidence

Summary of evidence: Many studies have recently shown that an impaired mucosal integrity is involved in the pathogenesis of GERD as well as in the generation of typical symptoms, particularly heartburn [150,313–317]. As a consequence, protection of esophageal mucosa (and restoration of mucosal integrity) is now emerging as a new therapeutic target for the management of GERD patients [219,318]. During the last decade, new medical devices containing hyaluronic acid in combination with different compounds (i.e. chondroitin sulphate, magaldrate, alginate) or herbal medicines (i.e. aloe vera, calendula) dispersed in a bioadhesive carrier to prolong their contact time with esophageal mucosa have been developed in order to protect the esophageal lining and improve esophageal mucosal defences against the noxious components of refluxate, including acid, pepsin and bile [319–326]. In particular, a class III medical device containing hyaluronic acid and chondroitin-sulphate demonstrated multiple functions in vitro, such as anti-inflammatory effect, wound repair, tissue regeneration and inhibition of tissue cytokine overexpression [320]. Two small prospective placebo-controlled studies showed that short-term treatment with this device achieved significant and quick symptom relief both in patients with erosive and non-erosive reflux disease [321,322]. More recently, a prospective, placebo-controlled RCT performed in NERD patients compared acid suppression with PPI alone or combined with mucosal protection with this medical device. The combined therapy, when extended for 14 days, was significantly more effective in relieving overall symptoms and improving the quality of life in the recruited patients compared to PPIs alone [323]. Moreover, the treatment was well tolerated, with no serious adverse events reported [323]. Another class III medical device, which combines hyaluronic acid and chondroitin sulfate with aluminum hydroxide, demonstrated - in an open-label uncontrolled study of GERD patients - improvements of both typical and extra-esophageal symptoms, as well as of some gastric juice biochemical parameters [319]. More recently, a 14-day treatment with the same medical device, in the form of melt-in-mouth tablets, showed efficacy in reducing GER-related symptoms in another open-label study involving patients who had not responded to PPI or alginate-based formulations [324]. No safety concerns were raised in both studies.

A novel patented medical device, an oral formulation containing hyaluronic acid, rice extract, and amino acids dispersed in a bioadhesive polymer matrix was evaluated in vitro and ex vivo models of esophageal mucosa damage. The results demonstrated its ability to reduce mucosal irritation caused by noxious agents, while also exhibiting soothing and reparative properties [325]. A single-centre, randomized, double-blind, parallel group, placebo-controlled clinical study was performed in 40 patients with typical GERD. At the end of treatment, 95 % of patients receiving the medical device achieved a three-point reduction in their total symptom score, compared to only 20 % in the placebo group. No adverse events were reported [326].

Finally, a recent RCT assessing the efficacy and safety of mucosal protective agent Poliprotect (a multi-herbal medical device) compared to omeprazole in the relief of heartburn and epigastric pain/burning. In this study, 275 endoscopy-negative outpatients were given a 4-week treatment with omeprazole (20 mg q.d.) or Poliprotect (5 times a day for the initial 2 weeks, followed by on-demand use). Afterward, all patients received an open-label, 4-week treatment period with Poliprotect on-demand [327]. The results showed that Poliprotect was non-inferior to standard-dose omeprazole in alleviating symptoms of heartburn and epigastric burning in patients without erosive esophagitis or gastroduodenal lesions [327].

In conclusion, esophageal mucosal protectants have shown promising results in the treatment of GERD, offering a significant advantage over PPIs by avoiding disruption of the gut microbiota [328]. The long-term consequences of PPI-induced microbiota changes are still not fully understood and may be deleterious. However, we are only at the beginning of a new therapeutic avenue for GERD, and more robust data from large, randomized controlled trials are needed to confirm these preliminary findings.

Statement 2.15: The Panel recommends FOR neuromodulator therapies in treating visceral hypersensitivity associated with GERD.
Statement endorsed, overall agreement: 91.30 %: *A* + 56.52 %, A 34.78 %, A- 4.35 %, D- 4.35 %, D 0 %, *D* + 0 %
LE: Weak Recommendation, very low level of evidence.

Summary of evidence: Visceral hypersensitivity is the enhanced perception of gastrointestinal stimuli, which occurs due to the sensitization of afferent nerves, spinal dorsal neurons, and alterations in psycho-neuroimmune interactions. This heightened sensitivity plays a role in symptom generation across various functional esophageal disorders, including GERD [329]. Within the GERD spectrum, different subtypes can be identified based on endoscopic appearance and reflux monitoring [201,2,11]. Specifically, RH is characterized by the absence of mucosal damage, normal esophageal acid exposure, and positive symptom association analysis or abnormal values of baseline impedance and PSPW-I [315,316,330,331]. Recent studies suggest that RH may either present as distinct entity or overlap with GERD, explaining why symptoms persist despite the normalization of reflux burden [332–335]. Low-dose neuromodulators are thought to lessen visceral nociception and it has been shown that they have a beneficial effect in other functional gastrointestinal disorders such as irritable bowel syndrome (IBS) [336]. Based on these data, it has been hypothesized that neuromodulators could similarly be useful in the treatment of symptoms related to esophageal hypersensitivity, in both functional esophageal disorders and GERD [268,337,338].

A systematic review by Weijenborg and colleagues identified 8 RCTs (n = 311 patients) evaluating the effect of different antide-

pressants (SSRIs, TCAs, SNRIs, SARIs) on functional chest pain, and 4 RCTs (n = 331) on GERD symptoms. Due to the clinical heterogeneity among the included trials, a meta-analysis of outcome data was not performed. Nevertheless, the authors concluded that antidepressant therapy led to a reduction in functional chest pain over a range from 18 % to 67 % and a reduction of heartburn in GERD patients, ranging from 23 % to 61 % [337]. One notable study by Viazis and colleagues who randomized 75 patients with RH from a cohort of 252 patients with PPI-refractory reflux symptoms. In this double-blind trial, patients were given citalopram (20 mg daily) for a period of 6 months. The study found that citalopram was significantly more effective than placebo in reducing reflux symptoms, with 38.5 % of the citalopram group reporting persistent GERD symptoms compared to 66.7 % in the placebo group [339]

More recently, a RCT was carried out in patients with established RH or functional heartburn based on endoscopy and reflux testing. Patients were randomly assigned to receive either once-daily imipramine 25 mg (n = 43) or placebo (n = 40) for 8 weeks [338]. The results showed that patients receiving imipramine did not achieve a higher rate of satisfactory relief of reflux symptoms than did those receiving placebo (45.5 vs. 41.2 %, respectively; odds ratio, 0.99; 95 % confidence interval 0.41–2.41). However, imipramine treatment led to a significant improvement of QoL (72±17 and 61±19, respectively; P = 0.048). Adverse events were similar in both groups. Finally, in a randomized trial comparing medical versus surgical therapy in treating PPI-refractory heartburn, confirmed by positive pH-impedance monitoring, some patients (N = 25) in the medical treatment group were treated omeprazole plus baclofen, with desipramine added depending on symptoms, and some other (N = 26) with omeprazole plus placebo. No significant difference in outcomes was seen between these two groups [268]. Overall, more controlled trials are needed to investigate the effects of neuromodulators on RH.

Statement 2.16: The Panel recognizes that complementary and alternative medicine (CAM therapy) might be useful in treating visceral hypersensitivity associated with GERD.
Statement endorsed, overall agreement: 84.60 %: *A* + 46.10 %, A 38.50 %, A- 7.70 %, D- 4.35 %, D 0 %, *D* + 3.85 %.
LE: Conditional recommendation, low level of evidence

Cognitive-behavioural therapy, combined with PPI therapy, may be helpful to improve quality of life in patients with non-erosive reflux disease [340]. In one study, patients with NERD and mood disorders were randomly assigned to three groups: a drug treatment group, a psychotherapy group, and a combined therapy group. All three treatments alleviated symptoms and improved quality of life to some degree, but the combined therapy group showed the most significant overall improvement [340]. Alternative treatments, such as acupuncture, have also been found to reduce heartburn in patients who do not respond to once-daily PPI therapy, particularly in those with functional heartburn or reflux hypersensitivity [341]. For example, Dickman et al. compared the effectiveness of acupuncture with doubling the PPI dose in 30 patients with GERD who had not experienced relief with once-daily PPI treatment. The acupuncture group showed significant reductions in daytime heartburn, nighttime heartburn, and acid regurgitation scores by the end of treatment (p < 0.001) [341].

In a study of 9 patients with FH, esophageal-directed hypnotherapy resulted in significant improvements in symptoms, visceral anxiety and quality of life. Alternative therapies targeting visceral hypersensitivity in GERD are an intriguing area of research. However, the lack of high-quality data and the heterogeneity of study populations limit the effectiveness and generalizability of these approaches [342].

Statement 2.17: The Panel recommends FOR lifestyle modifications and alginate/antiacids as first choice approach to GERD during pregnancy and lactation.
Statement endorsed, overall agreement: 86.96 %%: *A* + 69.56 %, A 17.40 %, A- 8.70 %, D- 0 %, D 4.35 %, *D* + 0 %.
LE: Strong Recommendation, moderate level of evidence.

Summary of evidence: Reflux symptoms occur in 30 %–50 % of pregnant women, with incidence rates reaching 80 % in some populations [343]. The main reasons are a decrease in LES pressure caused by sex hormones and mechanical factors (i.e. rise in intra-abdominal pressure due to a gravid uterus, abnormal gastric emptying and/or delayed small bowel transit).

Lifestyle modifications are considered the safest and first line treatment during pregnancy [343,344]. In general, it is advisable to wait until the end of the embryogenic period (from day 31 to day 71 from the last menstrual period) before starting drug therapy. However, if symptoms are troublesome and persistent, a pharmacologic treatment may be considered. Unfortunately, due to ethical and medico-legal problems, there are only a limited number of clinical studies, case reports and cohort studies that assessed the safety and efficacy of drugs during pregnancy.

First line pharmacological options typically include non-systemic drugs such as alginate, sucralfate or antacids, consisting of aluminium, calcium, or magnesium hydroxides. Antacids containing magnesium trisilicates should be avoided in high doses or for long-term therapy while those containing sodium bicarbonate are not recommended due to the risk of fluid overload and metabolic alkalosis [345–347].

H_2RAs are generally considered safe, with ranitidine being the only H_2RA whose efficacy during pregnancy has been well established [348]. Nizatidine is not recommended since human data are limited and animal studies have raised concerns about a higher risk of spontaneous abortion, congenital malformations and low birth weight [343,348].

PPIs have not been extensively studied in pregnancy and their efficacy and safety remain uncertain. They should be reserved for women with severe symptoms or GERD complications. Omeprazole is the only PPI classified as FDA category C due to potential fetal toxicity. A recent meta-analysis found that PPIs - when used at recommend doses – do not significantly increase the risk of major malformations [349].

Most drugs are excreted in breast milk. Aluminum and magnesium hydroxide antacids, being not absorbed, are not excreted in breast milk and are considered safe during lactation. Alginate and sucralfate have not been specifically studied during lactation, but they are assumed to be safe for the very limited (if any) maternal absorption. H_2RAs are safe, except nizatidine, whose breast milk concentrations are directly proportional to corresponding serum concentrations [350]. PPIs, due to their relatively low-molecular weight, are likely excreted into breast milk and are not recommended during lactation [343,351].

Statement 2.18: The Panel recommends FOR anti-reflux surgery in patients with refractory symptoms with objectively documented GERD and in patients responsive to medical therapy who are unwilling to take drugs or who are intolerant to them.
Statement endorsed, overall agreement: 91.30 %%: *A* + 56.52 %, A 34.78 %, A- 4.35 %, D- 0 %, D 4.35 %, *D* + 0 %.
LE: Strong recommendation, moderate level of evidence

Statement 2.19: The Panel recommends AGAINST anti-reflux surgery in patients with extra-esophageal symptoms of GERD, who do not respond to PPI therapy.

Statement endorsed, overall agreement: 91.30 %%: *A* + 56.52 %, A 34.78 %, A- 4.35 %, D- 0 %, D 4.35 %, *D* + 0 %.
LE: Conditional recommendation, low level of evidence

Statement 2.20: The Panel recommends FOR Roux-en-Y gastric bypass (RYGB) as an alternative measure to treat GERD in candidate obese patients, who are willing to accept its risks.
Statement endorsed, overall agreement: 91.30 %%: *A* + 56.52 %, A 34.78 %, A- 4.35 %, D- 0 %, D 4.35 %, *D* + 0 %.
LE: Conditional recommendation, low level of evidence.

Statement 2.21: The Panel recommends FOR laparoscopic anti-reflux procedures in patients with moderate GERD.
LE: Conditional recommendation, moderate level of evidence.
Statement endorsed, overall agreement: 91.30 %%: *A* + 56.52 %, A 34.78 %, A- 4.35 %, D- 0 %, D 4.35 %, *D* + 0 %.

Summary of evidence: Fundoplication is the well-recognized and standardized surgical treatment for GERD. Randomized studies and meta-analyses have shown that laparoscopic fundoplication should be preferred over the open procedure. While both methods have comparable efficacy, laparoscopic fundoplication has a lower mortality rate (0.04 % *vs* 0.2 %) and offers better cosmetic results [352].

Several studies have shown that laparoscopic fundoplication is highly effective in curing PPI-responsive GERD [352–357]. Long-term postoperative evaluations indicate 90 % and 80 % of patients experience persistent relief from heartburn and regurgitation at 10-year [353–356] and 20-year [352,356,357] follow-ups, respectively. Among those with recurrent heartburn, less than half show evidence of abnormal reflux [353]. A 2014 meta-analysis found that heartburn and regurgitation were less common in surgical patients compared to those on medical therapy. Although a considerable proportion of patients still required anti-reflux medications after fundoplication, surgical patients reported significantly higher satisfaction with their treatment in the short and medium term [358]. However, a recent Cochrane review raised concerns about the long-term benefit of laparoscopic fundoplication compared to ongoing PPI use, concluding that further RCTs are needed [359].

Compared with complete (360°) fundoplication (Nissen), partial fundoplications (e.g., Toupet and Dor) provide similar efficacy in relieving GERD symptoms, but are associated with less postoperative dysphagia, gas-bloat syndrome, and inability to belch and vomit [360–363]. However, partial fundoplication seems to have a higher rate of recurrences compared with the complete procedure [363].

Obese patients, who have a higher prevalence of GERD due the increased intra-abdominal pressure, are often considered for Roux-en-Y gastric bypass (RYGB). However, there are still several concerns regarding the anti-reflux procedures in the obese. While some studies showed poorer outcomes of fundoplication in obese patients compared to the non-obese ones [364] RYGB is a complex procedure with potential early and late complications. And, unfortunately, there are no RCTs directly comparing this operative approach with Nissen fundoplication [365].

Anti-reflux surgery has been used to treat patients with extra-esophageal GERD symptoms, though outcomes tend to be less favourable compared to those with typical GERD symptoms. Two systematic reviews assessing the relationship among extra-esophageal GERD symptoms, esophageal acid exposure, and surgical outcomes, reported a wide range of improvement, from 15 % to 95 % [366,367]. Recurrence of extra-esophageal symptoms after surgery is also a concern. A retrospective cohort study comparing adults with extra-esophageal GERD ($n = 36$) and typical reflux symptoms ($n = 79$), all of whom with abnormal distal esophageal acid exposure, showed that recurrence was more likely in patients with extra-esophageal symptoms and in those with poor response to preoperative PPI therapy [368]. Therefore, patients with extra-esophageal symptoms that do not respond to PPIs and those without objective evidence of reflux should avoid surgical or endoscopic treatment of GERD [368].

LINX™ (Torax Medical Inc., Shoreview, MN), a sphincter augmentation device, is a new laparoscopic anti-reflux procedure used to reinforce the cardias [369,370]. Feasibility trial with one- and 2-year follow-up evaluated the safety and efficacy of the procedure in patients with abnormal esophageal acid exposure (quantitated by 24-hour pH monitoring) and persistent typical GERD symptoms despite PPI use. At one year, 90 % of patients reported complete cessation of PPI use, and at two years, 86 % of patients remained off PPIs [371]. In another single-group evaluation of 100 patients with GERD before and after magnetic sphincter augmentation procedure, esophageal acid exposure decreased, reflux symptoms improved, and use of PPIs reduced [372].

Statement 2.22: The Panel recommends FOR Transoral Incisionless Fundoplication (TIF) only for patients with mild GERD (troublesome regurgitation or heartburn) without large (>2cm) hiatal hernia who are not willing to take PPIs or undergoing anti-reflux surgery.
Statement endorsed, overall agreement: 95.65 %: *A* + 60.87 %, A 34.78 %, A- 4.35 %, D- 0 %, D 0 %, *D* + 0 %
LE: Strong recommendation, moderate level of evidence
Statement 2.23: The Panel recommends AGAINST the use of the Medigus ultrasonic surgical endostapler (MUSE) in patients with GERD.
Statement endorsed, overall agreement: 95.65 %: *A* + 60.87 %, A 34.78 %, A- 4.35 %, D- 0 %, D 0 %, *D* + 0 %
LE: Strong recommendation, low quality of evidence

Statement 2.24: The Panel recommends AGAINST radiofrequency energy application as an alternative method to medical or surgical anti-reflux therapies. It may be used only in selected patients without erosive esophagitis and hiatal hernia to help relieve symptoms.
Statement endorsed, overall agreement: 95.65 %: *A* + 60.87 %, A 34.78 %, A- 4.35 %, D- 0 %, D 0 %, *D* + 0 %
LE: Weak recommendation, low quality of evidence

Statement 2.25: The Panel recommends AGAINST the use of anti-reflux mucosectomy (ARMS) in routine clinical practice in the treatment of GERD.
Statement endorsed, overall agreement: 95.65 %: *A* + 60.87 %, A 34.78 %, A- 4.35 %, D- 0 %, D 0 %, *D* + 0 %
LE: Strong recommendation, low quality of evidence

Summary of evidence: All studies on endoscopic procedures for treating GERD have excluded patients with hiatal hernias larger than 2 cm, LA grade C and D of EE, esophageal strictures, long-segment Barrett's esophagus. Based on these findings, endoscopic procedures should be avoided in these patients and should be reserved for those with milder forms of GERD.

Transoral incisionless fundoplication (TIF) is an endoscopic procedure performed with a suturing device and T-fasteners to create a gastroplication that reinforces the anti-reflux barrier. Some RCTs evaluated the efficacy of TIF, comparing it to a sham procedure, a sham procedure with PPIs or PPI therapy alone [373–377]. A meta-analysis of these RCTs showed that 66 % of patients treated with TIF had a significant clinical response (defined as at least 50 % improvement in GERD related quality of life (GERD-HRQL) or remission of heartburn and regurgitation) compared to 30 % in the control group [378].

The Medigus ultrasonic surgical endostapler (MUSE, *Medigus, Omer, Israel*) integrates flexible videoendoscopy with an ultrasonic rangefinder and a surgical stapler. In a prospective multicentre trial

Table 2
All statements with endorsement, level of evidence, grade of recommendation and agreement.

Section and Number	Statement/recommendation	Endorsement	Level of evidence	Grade of recommendation	Agreement
Section 1	**Diagnosis**	–	–	–	–
Section 1.1	The Panel recognizes that GERD should be suspected when patients refer heartburn and/or regurgitation twice or more weekly.	Yes	Moderate	Conditional	100 %
Section 1.2	The Panel recognizes that GERD is objectively defined by the presence of characteristic mucosal injury seen at endoscopy and/or abnormal oesophageal acid exposure demonstrated on a reflux monitoring study.	Yes	High	Conditional	100 %
Section 1.3	The Panel recommends FOR evaluating non-GERD causes in patients with extra-esophageal manifestations before attributing symptoms to GERD.	Yes	Moderate	Strong	100 %
Section 1.4	The Panel recommends FOR considering disorders of gut-brain interaction as functional heartburn and reflux hypersensitivity in patients with proven GERD and incomplete response to PPIs.	Yes	Low	Strong	95.65 %
Section 1.5	The Panel recommends FOR performing oesophageal impedance-pH monitoring ON PPIs for patients with an established diagnosis of GERD whose symptoms have not responded adequately to twice-daily PPI therapy.	Yes	Low	Strong	95.65 %
Section 1.6	The Panel recommends FOR using GERD-related questionnaires in clinical practice to evaluate clinical response to an appropriate GERD treatment.	Yes	Moderate	Moderate	91.30 %
Section 1.7	The Panel recommends FOR trying an empiric 8-week trial of PPIs once daily before a meal (30 min before breakfast) for patients with typical GERD symptoms (heartburn and regurgitation) who have no alarm symptoms.	Yes	Moderate	Strong	91.30 %
Section 1.8	The Panel recommends FOR an empiric PPI trial in patients with extra-esophageal GERD presentation only if typical symptoms are present or more.	Yes	Moderate	Strong	91.30 %
Section 1.9	The Panel recommends FOR an ambulatory reflux monitoring before empiric PPI therapy in patients with extraesophageal manifestations of GERD without typical GERD symptoms (e.g., heartburn and regurgitation).	Yes	Moderate	Strong	91.30 %
Section 1.10	The Panel recommends AGAINST routine urea breath testing or Helicobacter pylori stool antigen testing in all patients with GERD.	Yes	Low	Strong	82.61 %
Section 1.11	The Panel recommends AGAINST performing routine EGD in all patients with GERD symptoms.	Yes	Moderate	Strong	82.61 %
Section 1.12	The Panel recommends AGAINST routine mucosal sampling of the esophagus or gastro-esophageal junction in patients with heartburn and/or other symptoms suggestive for uncomplicated GERD and normal findings on endoscopy.	Yes	Moderate	Strong	82.96 %
Section 1.13	The Panel recommends FOR performing oesophageal manometry to appropriately locate the lower oesophageal sphincter and, therefore, correctly positioning pH or pH-impedance catheters.	Yes	Moderate	Strong	91.30 %
Section 1.14	The Panel recommends FOR performing oesophageal manometry to evaluate oesophageal peristaltic performance prior to any anti-reflux endoscopic or surgical procedure.	Yes	Low	Conditional	91.30 %
Section 1.15	The Panel recommends FOR oesophageal manometry combined with impedance in patients with suspected diagnosis of rumination syndrome and supragastric belching.	Yes	Moderate	Strong	91.30 %
Section 1.16	The Panel recommends FOR pH or impedance-pH monitoring in patients with reflux-like symptoms not responding to medical treatments, in patients with extra-esophageal symptoms, prior to anti-reflux endoscopic or surgical procedures, in patients with belching disorders and to diagnose functional heartburn and reflux hypersensitivity in patients not responding to medical treatment.	Yes	Moderate	Strong	100 %
Section 1.17	The Panel recommends AGAINST barium esophagram to diagnose GERD.	Yes	Moderate	Strong	91.30 %
Section 2	**Treatment**	–	–	–	–
Section 2.1	The Panel recommends FOR offering lifestyle advices (healthy eating, weight reduction in overweight and obese subjects, smoking cessation, avoidance of "trigger foods", avoiding meals within 2–3 h before bedtime) for GERD symptom control. Head of the bed elevation and nocturnal left lateral decubitus position may help some patients.	Yes	Low	Conditional	86.96 %
Section 2.2	The Panel recommends FOR a labelled-dose course of PPIs for 4–8 weeks, once daily before breakfast, in patients with symptoms of heartburn and regurgitation who have no alarm symptoms, and for 8-week in patients with erosive esophagitis.	Yes	Moderate	Strong	91.30 %
Section 2.3	The Panel recommends FOR a labelled-dose course of PPIs for 8–12 weeks in patients who have extra-esophageal and concomitant typical GERD symptoms.	Yes	Low	Conditional	91.30 %

(*continued on next page*)

Table 2 (*continued*)

Section and Number	Statement/recommendation	Endorsement	Level of evidence	Grade of recommendation	Agreement
Section 2.4	The Panel recommends FOR twice daily dose of PPIs in patients with GERD only if a concomitant Barrett esophagus is present, in proven laryngo-pharyngeal reflux or when there is no response or an incomplete response to once daily dose.	Yes	Low	Moderate	91.30 %
Section 2.5	The Panel recommends FOR switching to a different PPI regimen in patients with partial response to PPI treatment to improve symptom control.	Yes	Low	Weak	84.70 %
Section 2.6	The Panel recommends FOR continuous PPI maintenance treatment in patients with severe erosive GERD and/or Barrett's esophagus.	Yes	Moderate	Strong	95.65 %
Section 2.7	The Panel recommends FOR Continuous or cyclic PPI or on-demand maintenance treatment in patients with mild erosive GERD or PPI-responsive NERD whose symptoms recur at discontinuation.	Yes	Moderate	Strong	95.65 %
Section 2.8	The Panel recommends FOR the use of bedtime H_2-receptor antagonists in patients with GERD, particularly as *add-on* therapy, in those with persistent nocturnal symptoms and in those with objective evidence of nocturnal acid reflux on pH monitoring despite PPI treatment.	Yes	Low	Weak	86.96 %
Section 2.9	The Panel recommends FOR the use of prokinetic agents as add-on therapy for patients with GERD with concomitant symptoms suggestive of delayed gastric emptying.	Yes	Moderate	Conditional	84.70 %
Section 2.10	The Panel recommends FOR the use of baclofen for patients with refractory GERD. However, its use should be carefully considered and monitored due to the high rate of adverse effects.	Yes	Moderate	Moderate	86.96 %
Section 2.11	The Panel recommends FOR the use of P-CABs as treatment of gastro-esophageal reflux disease.	Yes	Moderate	Strong	95.65 %
Section 2.12	The Panel recommends FOR the use of antacids and sucralfate as treatment of GERD symptoms.	Yes	Very low	Weak	86.96 %
Section 2.13	The Panel recommends FOR the use of alginate-containing formulations as treatment of GERD.	Yes	Moderate	Strong	91.31 %
Section 2.14	The Panel recommends FOR the use of esophageal mucosal protectants as add-on treatment of GERD.	Yes	Low	Weak	82.61 %
Section 2.15	The Panel recommends FOR neuromodulator therapies in treating visceral hypersensitivity associated with GERD.	Yes	Very low	Weak	91.30 %
Section 2.16	The Panel recognizes that complementary and alternative medicine (CAM therapy) might be useful in treating visceral hypersensitivity associated with GERD.	Yes	Low	Conditional	84.60 %
Section 2.17	The Panel recommends FOR lifestyle modifications and alginate/antiacids as first choice approach to GERD during pregnancy and lactation.	Yes	Moderate	Strong	86.96 %
Section 2.18	The Panel recommends FOR anti-reflux surgery in patients with refractory symptoms with objectively documented GERD and in patients responsive to medical therapy who are unwilling to take drugs or who are intolerant to them.	Yes	Moderate	Strong	91.30 %
Section 2.19	The Panel recommends AGAINST anti-reflux surgery in patients with extra-esophageal symptoms of GERD, who do not respond to PPI therapy.	Yes	Low	Conditional	91.30 %
Section 2.20	The Panel recommends FOR Roux-en-Y gastric bypass (RYGB) as an alternative measure to treat GERD in candidate obese patients, who are willing to accept its risks.	Yes	Low	Conditional	91.30 %
Section 2.21	The Panel recommends FOR laparoscopic anti-reflux procedures in patients with moderate GERD.	Yes	Moderate	Conditional	91.30 %
Section 2.22	The Panel recommends FOR Transoral Incisionless Fundoplication (TIF) only for patients with mild GERD (troublesome regurgitation or heartburn) without large (>2 cm) hiatal hernia who are not willing to take PPIs or undergoing anti-reflux surgery.	Yes	Moderate	Strong	95.65 %
Section 2.23	The Panel recommends AGAINST the use of the Medigus ultrasonic surgical endostapler (MUSE) in patients with GERD.	Yes	Low	Strong	95.65 %
Section 2.24	The Panel recommends AGAINST radiofrequency energy application as an alternative method to medical or surgical anti-reflux therapies. It may be used only in selected patients without erosive esophagitis and hiatal hernia to help relieve symptoms.	Yes	Low	Weak	95.65 %
Section 2.25	The Panel recommends AGAINST the use of anti-reflux mucosectomy (ARMS) in routine clinical practice in the treatment of GERD.	Yes	Low	Strong	95.65 %

Abbreviations: NA: not available: unable to assess using GRADE methodology.

involving 66 patients who underwent MUSE procedure, the GERD-HRQL score improved by more than 50 % at 6 months. In addition, 73 % of patients were able to stop PPI therapy and 64.6 % of patients were no longer using daily antisecretory medication [379]. Severe complications, including empyema and haemorrhage, occurred in two patients. In another small retrospective study, MUSE (in 11 patients) was compared to laparoscopic fundoplication (performed in 16 patients). A hiatal hernia larger than 3 cm was an exclusion criterion for MUSE procedure. After a 6-month follow-up, laparoscopic fundoplication appeared more effective and one severe complication (esophageal perforation) was reported in the MUSE group [380]. Overall, data on the safety and efficacy of MUSE in the treatment of GERD are limited and RCTs are still lacking.

Table 3
Summary of available surgical/endoscopic procedures for GERD treatment.

Procedure	Consensus (FOR/AGAINST)	Explanation
Nissen Fundoplication	FOR	Gold standard surgical approach; effective for severe GERD and refractory cases.
Toupet Fundoplication	FOR	Partial fundoplication with lower dysphagia risk; recommended for patients with esophageal motility disorders.
Magnetic Sphincter Augmentation (MSA)	FOR	Less invasive alternative with promising results; suitable for patients unwilling to undergo fundoplication.
Transoral Incisionless Fundoplication (TIF)	FOR	Minimally invasive endoscopic technique; effective in selected patients with mild-moderate GERD.
Radiofrequency Application (Stretta)	AGAINST	Limited supporting evidence; high variability in outcomes, not recommended outside clinical trials.
Anti-reflux Mucosectomy (ARMS)	AGAINST	Still experimental with limited data; not recommended outside research settings.
Medigus Ultrasonic Surgical Endostapler (MUSE)	AGAINST	Limited evidence and concerns regarding durability; not recommended outside clinical trials.

Radiofrequency energy application to the LES (Stretta, *Respiratory Technology Corporation, Houston, Texas*) is an endoscopically-guided procedure in which radiofrequency current is delivered by a series of radially arranged needles placed over the esophagogastric junction (EGJ). Radiofrequency energy application, which is unavailable in some countries, is not recommended in patients with erosive esophagitis or hiatal hernia. Four RCTs (three comparing radiofrequency energy application with sham therapy [381–383], and one comparing radiofrequency energy application with PPI therapy [384]) showed an overall low efficacy. Results from these RCTs demonstrated some significant short-term improvement in symptom burden and quality of life, but long-term data are still lacking. The meta-analysis performed by Fass et al., including both RCTs and cohort studies, concluded that radiofrequency energy application is modestly effective in improving both objective and subjective clinical endpoints, though it does not significantly increase basal LES pressure [385].

Anti-reflux mucosectomy (ARMS) is an endoscopic mucosal resection (EMR) performed at the level of the cardia, covering 180° – 270° of the circumference. Only three single-arm interventional studies, involving a total 39 PPI-refractory GERD patients without a sliding hernia or with a hernia no larger than 2 cm, have been published. These studies reported a clinical response in 69 % – 80 % of patients, with dysphagia occurring in 13 % [181–183]. However, controlled data are lacking, and the small sample sizes of the published studies make it difficult to draw definite conclusions about safety and efficacy of ARMS. As a consequence, this – like the other endoscopic procedures - should not be used outside clinical trials and are not recommended for current clinical practice.

Table 3 summarises all the available surgical/endoscopic procedures for GERD treatment.

4. Conclusion

GERD is a highly prevalent clinical condition that significantly impacts both the physical and psychological well-being of patients. This national, multidisciplinary group of Italian experts used a Delphi process to summarize and grade the current consensus on the diagnosis and treatment of this condition. The Consensus Group reviewed and voted on various statements to guide specialty physicians and general practitioners in the management of GERD in clinical practice.

Specific author contributions

All the authors contributed with data collection and analysis, writing of the manuscript, approving final version. EVS, BB, CS, MP, GS edited the final version of the manuscript.

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None.

Conflict of interest

Edoardo Vincenzo Savarino: Edoardo Vincenzo Savarino has served as speaker for Abbvie, Abivax, Agave, AGPharma, Alfasigma, Apoteca, Biosline, CaDiGroup, Celltrion, Dr Falk, EG Stada Group, Fenix Pharma, Galapagos, Johnson&Johnson, JB Pharmaceuticals, Innovamedica/Adacyte, Eli Lilly, Malesci, Mayoly Biohealth, Montefarco, Novartis, Omega Pharma, Pfizer, Rafa, Reckitt Benckiser, Sandoz, Sanofi/Regeneron, SILA, Sofar, Takeda, Tillots, Unifarco; has served as consultant for Abbvie, Agave, Alfasigma, Biogen, Bristol-Myers Squibb, Celltrion, Dr. Falk, Eli Lilly, Fenix Pharma, Ferring, Giuliani, Grunenthal, Johnson&Johnson, JB Pharmaceuticals, Merck & Co, Nestlè, Pfizer, Reckitt Benckiser, Sanofi/Regeneron, SILA, Sofar, Takeda, Unifarco; he received research support from Bonollo, Difass, Pfizer, Reckitt Benckiser, Sanofi/Regeneron, SILA, Sofar, Unifarco, Zeta Farmaceutici.

Brigida Barberio: has served as speaker for Abbvie, Agave, Alfasigma, AGpharma, Janssen, Eli Lilly, MSD, Pfizer, Sofar, Takeda, Unifarco; has served as consultant for Abbvie and Janssen.

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Antonio Pisani: none

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Vincenzo Savarino: has served as speaker for Malesci, Grunenthal, Takeda and Alfasigma

Carmelo Scarpignato: has served as a speaker, consultant, and/or advisory board member for Alfasigma, Pfizer, Takeda, Reckitt Benckiser, and Shionogi, and has in the past received funding from Giuliani Pharmaceuticals and Pfizer.

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Supplementary materials

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