An Overview of Gastroesophageal Reflux Disease

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Definition and Clinical Manifestations

Gastroesophageal reflux disease (GORD) is a chronic disorder that is caused by abnormal reflux. It is associated with prolonged exposure of the distal oesophagus and extra oesophageal airways to gastric contents and leads to cardinal symptoms and/or findings, which affect patient quality of life [1]. Typical GORD symptoms include heartburn (usually defined as a rising retrosternal burning discomfort) and/or regurgitation, and atypical symptoms include laryngopharyngeal and pulmonary symptoms, such as cough and non-cardiac chest pain (Fig. 2.1) [2].

From a physician's point of view, the classic GORD patient has typical symptoms, with a satisfactory proton pump inhibitor (PPI) response and/or erosive oesophagitis. Many clinicians believe that the diagnosis of GORD should be primarily based on the presence of these typical symptoms. The specificities of heartburn and acid regurgitation for GORD were found very high in early studies such as 89% and 95%, respectively [3]. However, latest studies concluded that it is not possible to identify reflux disease reliably with symptom questionnaires alone.

In the disease spectrum, there are more caveats rather than a clear-cut diagnosis, particularly in three clinical conditions or in a combination of these conditions:

1. patients with normal endoscopy,
2. PPI unresponsiveness, and
3. the presence of extraoesophageal symptoms, without typical symptoms.

GORD affects not only the oesophagus but also the upper airway, and it is associated with a wide range of extraoesophageal symptoms; therefore,

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A. H. Morice, P. W. Dettmar (eds.), *Reflux Aspiration and Lung Disease*,
https://doi.org/10.1007/978-3-319-90525-9_2

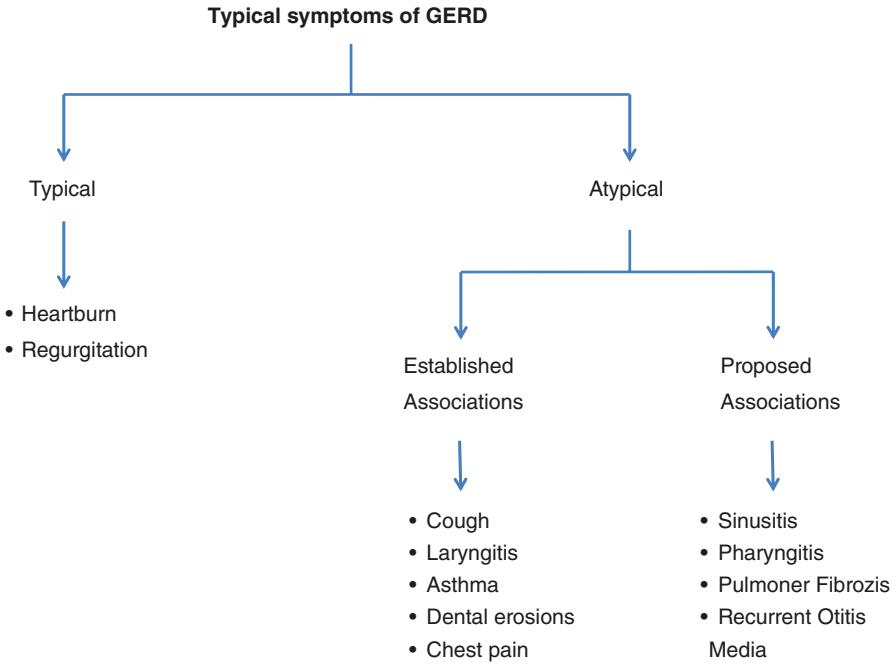

Fig. 2.1 Typical symptoms of GERD [2]

treating the disease requires collaboration between different disciplines, including gastroenterology, ENT, pulmonary medicine, general surgery, paediatrics, internists and GPs. Thus, a GORD diagnosis might be more difficult because typical symptoms cannot be observed in most patients with extraoesophageal symptoms.

Epidemiology

Gastroesophageal reflux disease (GORD) is one of the most common chronic diseases in adults in developed countries. If all studies from Western countries were evaluated cumulatively, the prevalence of heartburn and acid regurgitation would be 23% and 16%, respectively [4]. High-quality prevalence studies from Western countries have been performed since the 1990s; such studies have been performed only since the 2000s in Eastern countries. The majority of studies from Eastern countries have been performed in South-East and East Asian populations, and the prevalence of GORD in these populations is 2.5–8.2%, which is markedly lower than that in Western studies (Table 2.1) [1, 4].

According to epidemiological studies, one major difference between Western and Eastern countries is the prevalence of typical GORD symptoms. Patients in Western countries primarily exhibit heartburn, whereas patients in most other

Table 2.1 The prevalence of GERD and typical symptoms in studies performed using the Mayo Questionnaire [1]

Place	Author	No of subjects	Heartburn	Regurgitation	GERD
Olmsted (USA)	Locke	1511	17.8	6.3	19.8
Moscow (Russia)	Bor, Lazebnik	1065	17.6	17.5	23.6
Turkey	Bor	3214	9.3	16.6	22.8
Argentina	Chiocca	839	16.9	16.5	23
Eastern Iran	Vossoughinia	1637	NA	25.7	25.7
Olmsted (USA)	Jung	2273	NA	NA	18
Philadelphia (USA)	Yuen	1172	NA	NA	26.2
Madrid (Spain)	Rey	709	NA	NA	8.5
Spain	Diaz-Rubio	2500	NA	NA	9.8
China	Wong	2209	NA	NA	2.5

Table 2.2 The prevalence of additional symptoms in studies performed using both the same questionnaire and the same diagnostic criteria [6]

	Olmsted (USA)	Moscow (Russia)	Izmir (Turkey)	Argentina	NW China
NCCP	23.1	15.5	37.3	37.6	34.7
Dysphagia	13.5	25.5	35.7	26.8	6.5
Odynophagia	–	34.4	35.7	–	10.7
Globus	7.0	25.5	23.8	26.3	15.2
Dyspepsia	10.6	60.2	42.1	38.7	29.3
Belching	–	43.0	24.6	–	–
Nausea	–	53.8	60.3		–
Vomiting	–	29.1	38.1	–	–
Hiccup	–	6.8	9.5	–	–
Cough	–	36.7	19.8	–	8.9
Asthma	9.3	–	0.8	6.7	4.2
Pharyngeal symptoms and hoarseness	14.3	10.4	28.6	21.8	9.4

countries predominantly show acid regurgitation [5, 6]. These differences are likely underestimated; however, it is important because regurgitation itself represents a different therapeutic profile compared to heartburn. For example, proton pump inhibitors are less effective compared to heartburn and other medications; motility agents, alginate or other modalities (surgery) might be more effective.

No study has directly compared the atypical symptoms found in different countries, but studies using the same questionnaire have yielded different results. For example, the prevalence of asthma among GORD patients ranges from 0.8% to 9.3%. The prevalence of other symptoms, such as dyspepsia, also differs (range, 10.6–60.2%) (Table 2.2) [6]. There is a strong need for more studies addressing the incidence of the disease, as well as patient quality of life.

Diagnosis

Currently, different GORD features are measured with different tests, and there is no gold standard used to diagnose the full spectrum of the disease. Some tests have been nearly abandoned, such as radionuclide scintigraphy and the Bernstein test. Others might lose their practicality because of further developments, such as catheter-based 24 h intraoesophageal pH monitoring, barium swallow radiology, and 24 h intraoesophageal bilirubin detection (Bilitec). New and exciting tests are replacing some of these modalities, such as catheter-based intraoesophageal 24 h intraoesophageal pH/impedance monitoring, high resolution manometry, etc. [7]. Some diagnostic tests are under evaluation, with different expectation levels, such as pepsin detection in the saliva (Peptest), mucosal impedance measurements, and laryngeal pH monitoring (Restech). The advantages and disadvantages of different tests are summarized in the Table 2.3.

Table 2.3 Summary of diagnostic tests in gastroesophageal reflux disease

Test	Pros	Cons
24 h intraesophageal pH monitoring	Quantifies refluxed acid, allows for determination of acid and symptom correlation	Normal even in 30% of erosive esophagitis patients, catheter base, patient discomfort effects the quality of the measurement, acid reflux does not mean the mucosal damage, inter/intra observer variabilities are too high
24 h intraesophageal pH/impedance monitoring	Allows to measure weak or nonacid refluxes. Basal mucosal impedance is a new promising metric. More sensitive determination of all types of reflux and symptom correlation	Catheter base, patient discomfort effects the quality of the measurement. More expensive, less experience. Needs manual analysis especially for research.
Wireless pH monitoring	Better tolerance. Allows longer measurements (days), if off-PPI measurement shows pathologic reflux, PPI therapy can be initialized and allows to on-PPI measurement	Needs endoscopy, more expensive
Conventional manometry	LES localization for catheter-based monitoring systems, exclude esophageal motility disorders	Catheter base, measures lower esophageal sphincter pressure but the role for GERD is unclear
High resolution manometry	Very sensitive to detect HH, motility disorders, esophagogastric junction outflow obstructions. New metrics to detect GERD and combination with other technologies (impedance, ultrasound) are promising	Catheter base. Still needs improvements for the criteria and metrics

Proton Pump Inhibitor Trial

Many centres worldwide lack sophisticated diagnostic modalities; therefore, they rely on patient symptoms and upper gastrointestinal endoscopy. The PPI response to typical symptoms is a primary diagnostic tool [8]. However, the PPI response of patients with typical symptoms is approximately 60–65% for heartburn and <50% for regurgitation, and this low response rate decreases the value of the therapeutic trial approach. Recently, all PPI trial studies have been evaluated by the Turkish GORD consensus group [9], which found 16 studies (seven omeprazole, five lansoprazole, two esomeprazole, two rabeprazole). As shown in the table, most of these studies used a high dose (double) of PPI, and the median time was 14 days. There was no consensus for the dose, time of the trial or definition of the "response" (Table 2.4). Despite the heterogeneous design of these studies, the following observations can be asserted;

- The cumulative sensitivity of the PPI trial is 82.3%, and the specificity is 51.5%. The positive predictive value is 79%, and the negative predictive value is 56.9%. These figures indicate that most GORD patients responded well to the PPI trial; however, a negative test does not exclude the possibility of disease. Indeed, the RCT evidence suggests that the effect of PPI is similar to placebo for airway symptoms.
- Patients with erosive oesophagitis and pathologic acid reflux have a greater chance of response, although these groups do not need a PPI trial.

Table 2.4 PPI trial studies [9]

Study	PPI	Dose	Time (days)	n=
1. Fass (1998)	Omeprazole	40 mg AM and 20 mg PM	7	37
2. Pandak (2002)	Omeprazole	20 mg AM and PM	14	38
3. Xia (2003)	Lansoprazole	30 mg AM	28	36
4. Bautista (2004)	Lansoprazole	60 mg AM and 30 mg PM	7	40
5. Pace (2010)	Omeprazole	20 mg AM and PM	15	544
6. Dent (2010)	Esameprazole	40 mg AM	14	296
7. Cho (2010)	Lansoprazole	30 mg AM and 30 mg PM	14	73
8. Kim (2009)	Rabeprazole	20 mg Am and 20 mg PM	14	42
9. Aanen (2006)	Esameprazole	40 mg AM	13	67
10. Dekel (2004)	Rabeprazole	20 mg AM and PM	14	14
11. Bate (1999)	Omeprazole	40 mg AM	14	58
12. Fass (2000)	Omeprazole	40 mg AM and 20 mg PM	14	14
13. Juul-Hansen (2001)	Lansoprazole	60 mg AM	5	56
14. Schenk (1997)	Omeprazole	40 mg AM	14	41
15. Juul-Hansen (2003)	Lansoprazole	60 mg AM	7	52
16. Fass (1999)	Omeprazole	40 mg AM and 20 mg PM	7	42

- Non-cardiac chest pain patients are one of the best candidates, if their pain is related to acid reflux.
- *The suggested therapeutic trial is 2 weeks for a double dose of PPI, and the response should be >50% healing of symptoms. It still must be determined which symptoms should be considered: heartburn, regurgitation or both?*

Upper Gastrointestinal Endoscopy

Upper gastrointestinal endoscopy (UGIE) is the most commonly used diagnostic technique. It is an important tool to determine whether the phenotype of the disease is NERD or erosive oesophagitis. UGIE detects oesophagitis, strictures and Barrett's oesophagus. It also allows to take biopsy, particularly for the diagnosis of eosinophilic oesophagitis, and it is useful for differential diagnoses, particularly in PPI refractory patients. However, in patients with non-peptic symptoms, the yield is low.

LA Grades C, D and possibly B oesophagitis are sufficient for the diagnosis [10]. However, note that oesophagitis A can be observed in a minority of asymptomatic patients. Oesophageal histology has limited value except for Barrett's oesophagus and eosinophilic oesophagitis. Narrow band imaging, confocal laser endomicroscopy and similar new endoscopic techniques do not add more information to the diagnosis [11]. Dilated intercellular spaces and microscopic oesophagitis are observed more in NERD and ERD; however, routine biopsy of the oesophagus and histopathology are not recommended.

Indications for First Upper Gastrointestinal Endoscopy

- Upper gastrointestinal tract cancer or Barrett's oesophagus in first-degree relatives.
- Alarm symptoms; dysphagia, odynophagia, unexplained weight loss, anaemia, vomiting.
- If peptic symptoms start in patients older than 50 years of age.
- A symptom duration >5 years.
- A <50% response rate after 8 weeks of PPI therapy.

Indications for Follow-Up Upper Gastrointestinal Endoscopy

- The presence of Barrett's oesophagus.
- In patients with severe erosive oesophagitis: after high-dose PPI therapy for 4–8 weeks to evaluate for possible Barrett's oesophagus.

24-h Ambulatory pH or pH-Impedance Monitoring

Traditionally, 24-h pH monitoring has been accepted as the gold standard diagnostic method for GORD. Although this technique is important, "the gold standard" concept is questionable. A 24-h conventional pH testing failed to diagnose abnormal

acid exposure in up to 40% of patients with erosive oesophagitis when the percentage total time for pH < 4 was used as the only criterion. This technology has many limitations. It measures only acid reflux episodes; however, weak and possibly non-acid reflux episodes might be responsible for some symptoms, particularly in patients with extraoesophageal symptoms or PPI refractories. Indeed, it has been suggested that acidic reflux is not the major precipitant of airway disease. Patients cannot maintain their regular daily activities and having meals with a catheter in their noses and throats. The day-to-day variation is high, and only reflux at the fifth centimeter within the oesophagus is measured. Lack of a diagnostic gold standard for gastroesophageal reflux disease is also a problem when measuring the exact sensitivity and specificity of the technique. Therefore, there is a strong need for better technologies [7].

Recently, a new technology was added for pH-monitoring, and now we have 24-h impedance-pH monitoring. This technology allows the detection of acidic, weakly acidic, and non-acid reflux, as well as liquid and gaseous refluxates [10]. There is still a strong need for more healthy control studies with equipment from different companies to detect normative thresholds. Many new metrics have been proposed over the years; however, baseline impedance is a good reflection of mucosal integrity and can be used. However, low baseline impedance makes it difficult to interpret pH-impedance studies. Automated analysis may be sufficient; however, in the case of a significant number of weak and/or non-acid reflux events, it is advisable to perform a manual analysis. Addition to these major metrics, it is important to evaluate the symptom-reflux association [12].

Symptom-reflux association is an interesting approach to diagnose some GORD phenotypes, such as oesophageal hypersensitivity and functional heartburn. Currently two metrics are used: symptom index and symptom association probability.

$$\textit{Symptom index} = \textit{number of reflux} - \textit{related symptom episodes} / \left(\textit{total number of symptom episodes}\right) \times 100$$

Symptom association probability is calculated by dividing the 24-h data into 2-min segments. Then, for each 2-min segment, it is possible to determine whether the reflux occurred and a symptom was reported. At least three events per symptom episode must be reported to calculate these tests.

These tests should be used together, and if two metrics are positive, then the diagnosis is oesophageal hypersensitivity; if the metrics are negative, then the diagnosis is functional heartburn.

Indications for 24-h Impedance-pH Monitoring

- Patients with non-erosive reflux disease and who are refractory to PPI therapy (the procedure should be performed off-PPI in patients with no response at all. However, an on-PPI test is suggested for patients who demonstrate a partial response).
- Extraoesophageal symptoms, particularly cough, to identify the reflux-cough relationship (pharyngeal pH measurements are possibly not useful).
- Belching and rumination.

- Select patients undergoing anti-reflux surgery and with post-fundoplication symptoms.
- Evaluation of anti-reflux treatment failure.
- Non-cardiac chest pain.

Wireless pH Monitoring

In this capsule-based study, the placement of the wireless pH capsule was performed in the outpatient endoscopy unit, following an upper GI endoscopy.

The distance from the incisors to the oesophagogastric junction was measured during the upper GI endoscopy, then the endoscope was removed, and the capsule was transorally advanced with an applicator deployed 6 cm proximal to the junction. It measured the pH level until the capsule fell, which generally took 2–9 days. This procedure is preferable in patients who are intolerant of a catheter-based measurement. When the symptom-reflux relationship occurs is important; however, symptoms (such as NCCP) rarely occur. Therefore, it is preferable to measure them for as long as possible. In our department, we prefer to analyse the data on a daily basis, and when sufficient evidence is obtained for a GORD diagnosis, the PPI therapy is immediately initiated to observe the PPI response. The major drawbacks of the procedure are the cost and need for an upper GI endoscopy [13, 14].

Oesophageal Manometry

Oesophageal manometry does not have any direct diagnostic value for GORD; however, it has different utilizations to support the diagnosis. Patients who are refractory to PPIs should be evaluated to eliminate other diseases, such as achalasia and other motor disorders of the oesophagus. Other indications are preoperative evaluation of the patient and localization of LES for the placement of pH catheters.

New technologies, such as high-resolution manometry, have a higher diagnostic value than conventional manometry and should be preferred. Indeed, some patients with ‘idiopathic’ airway symptoms have been diagnosed with oesophageal dysmotility. This technology can be used to assess the size of the hiatal hernia, as well as the peristaltic reserve [15].

Other Tests

A barium swallow and scintigraphy cannot be recommended to diagnose GORD. Endoluminal functional lumen imaging probe (Endo FLIP) is a new diagnostic tool that can be used to measure the distensibility of LES. Achalasia dilatation and anti-reflux fundoplication are possible indications for the technique; however, its value is not established yet for the diagnose of the disease. The measurement of pepsin in the saliva is a promising tool and will be discussed in the following chapters.

Medical, Endoscopic and Surgical Therapy

The major aim of current GORD therapy is symptom relief. The possibility of curing symptoms is low, which increases the importance of GORD-related quality of life as a major therapeutic target.

Lifestyle Modifications

Despite their common use, lifestyle modifications have limited effects but should be advised according to a patient's history and experience [16, 17]. If a patient defines some foods or drinks responsible for symptoms, a particular dietetic modification can be arranged. According to the meta-analysis, only some modifications are significant;

- Obesity is one of the most important factors, and losing weight is crucial. The association between obesity and GORD was evaluated in a systematic review, which found a positive association between a BMI > 25 kg and GORD symptoms (odds ratio 1.43, 95% CI 1.16–1.77). A similar increase was also shown for oesophagitis and obesity (1.76, 1.16–2.68) [18].
- Chocolate, fatty food, sodas should be avoided. Salt and white-wheat bread might be related to symptoms. Personal differences are encountered with different foods.
- Low volume, protein-rich and high-fibre food should be preferred. Controlled data, however, are greatly lacking and inconclusive [19].
- Heavy exercise might increase the risk.
- Smoking, in terms of the consumption rate, is a risk factor that has been reported in basic science and epidemiologic studies. Alcohol consumption is noxious on the oesophageal epithelium in basic science studies; however, the risk is unclear in epidemiologic studies. The cessation of both is advisable [20].
- Left lateral position and head elevation are important to protect against nighttime reflux but difficult to adapt and disruptive to the quality of sleep [21]. Their long-term effects are not clear.

Interestingly and contrary to dogma, the speed of eating does not impact reflux episodes in normal weight [22] and obese populations [23].

Medical Therapy

GORD medications can be classified as follows:

I Acid neutralization or inhibition:
1. Antacids neutralize secreted acids and are primarily used for mild peptic symptoms. The onset of action is rapid; however, the effects are short lived. Despite the widespread use of antacids, even the studies compared to placebo

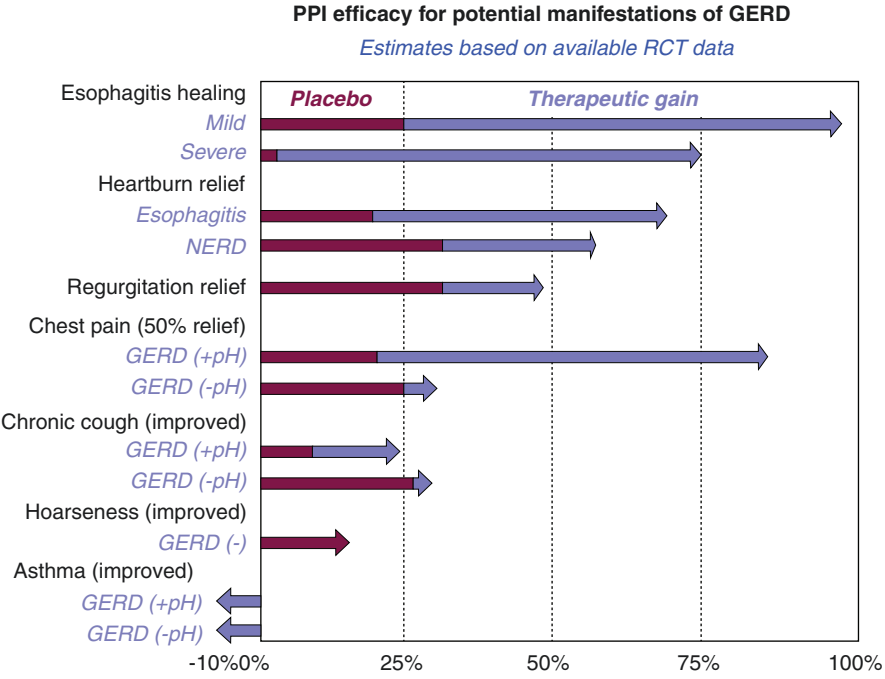

Fig. 2.2 PPI efficacy for potential manifestations of GERD [28]

provided conflicting results. Their therapeutic benefit in the treatment of GORD is limited by the lack of well-designed, large, placebo-controlled trials. Thus, it is unlikely that these drugs will have a major effect on the disease [24]. Because they act locally, antacids are considered to be a first line therapy with alginates for GORD in pregnancy [25]. However, magnesium-containing agents should be avoided, and calcium content should be taken into consideration especially for the overdose.

2. H2 receptor antagonists inhibit acid production in the parietal cell on H2 receptors. Cimetidine, ranitidine, famotidine, and nizatidine are still widely use worldwide, particularly for night-time reflux, because of their inhibitory effect on basal acid stimulation [17]. All H2RAs have a similar efficacy in symptom relief and the healing of oesophagitis. This drug group has a good safety record, with few side effects. However, some limitations exist, such as a relatively short duration of action, incomplete inhibition of meal-induced acid secretion, and the development of tolerance (as common as 50% within 2 weeks, possibly related to the down-regulation of H2-receptors) [26].
3. Proton pump inhibitors irreversibly inhibit acid secretion through H+/K+ adenosine triphosphatase (ATPase), the proton pump of the parietal cell responsible for acid production. They have superior efficacy compared to histamine H2 receptor antagonists and are currently the most effective therapeutic option [27]. The healing rates for oesophagitis are summarized in Fig. 2.2 [28]. According to

Table 2.5 The possible reasons for the ineffectuality of PPIs

• Diagnostic problems such as functional dyspepsia, IBS, cancers, achalasia, eosinophilic esophagitis
• Compliance problems such as postprandial consumption of medications
• Inadequate dosing
• Acid regurgitation
• Fast metabolizers
• Concomitant medications
• Malabsorptions,
• Hypersensive oesophagus, functional heartburn
• Weak/nonacid reflux
• Pscyhiatric comordidities, fear of cancer
• PPI resistance in time
• Delayed gastric emptying, gastric outflow obstructions
• Gastric acid hypersecretion
• Extraesophageal symptoms
• Nocturnal acid breakthrough

the standard dose treatment, compared to placebo, the highest response rate can be achieved with mild oesophagitis. In terms of heartburn relief, patients with oesophagitis have a higher success rate compared to non-erosive reflux patients [17]. However, it should be noted that the PPI unresponsiveness rate reaches 30–40% in erosive or NERD groups [29]. Regurgitation, which is the most common symptom in non-Western countries, has an even lower response rate (<50%) [30]. The lowest response rates are seen for extraoesophageal symptoms, such as hoarseness, asthma and chronic cough. The possible reasons for the ineffectuality of these drugs are summarized in Table 2.5. The complications of long-term PPI consumption are always worrying [31]. Of the many possible side effects, only a minority has been found to be significant: bone fractures (osteoporosis), clostridium difficile infection, bacterial overgrowth, and spontaneous bacterial peritonitis. The latter has the highest risk. This is a hot topic now, and many new studies are being published. Patients who need these drugs for long-term or continue therapy should be monitored carefully. However, there is no consensus on the concept of "long-term" therapy in terms of time and dosage.

II Barrier forming agents, such as alginate-based formulations, appear to act through a unique mechanism, a mechanical barrier. In the presence of gastric acid, alginates precipitate, forming a gel. In the presence of gastric acid, bicarbonate is converted to carbon dioxide, which becomes entrapped within the gel precipitate and converts into foam, floating on the surface of the gastric contents, much like a raft on water [32]. The alginate-based raft remains in the upper part of the stomach, suppressing the acid pocket [33]. It also binds or filters pepsin and bile, removing them from the refluxate. These drugs primarily reduce acid and then non-acid reflux events (and on the height of proximal extent of reflux events along the oesophagus in some studies). However, the gaseous component of reflux is not controlled [34].

III Prokinetic agents increase lower oesophageal sphincter pressure, accelerate gastric emptying, and increase the amplitude of oesophageal contractions. Their effects vary from one agent to another. The adverse-event profile of these agents must be weighed against any clinical benefit and most classical agents, such as bethanechol, metoclopramide, domperidone, and cisapride, either out of market or under supervision (by reason of cardiac side effects, particularly fatal arrhythmia). However, safety studies, particularly those with domperidone, are questionable and clearly metoclopramide is much riskier [35]. Care should be taken in patients older than 65 years of age; long QT syndromes or medications prolong the QT, with arrhythmia, >30 mg/day.

IV Mucosal protectives. Sucralfate, is a mucosal-protective agent that binds to inflamed tissue, producing a protective barrier, inhibiting the noxious effects of pepsin and bile. GORD studies are limited, with small numbers of participants, primarily compared to placebo [36]. Because of the high confidence interval, the effect is not superior to placebo. Currently, its use is limited to GORD in pregnancy, pill oesophagitis, caustic ingestion, etc.

V Other options. Tricyclic antidepressants and selective serotonin reuptake inhibitors can be used in some subgroups, such as oesophageal hypersensitivity and functional heartburn [17]. This is a new and exciting era for these GORD phenotypes.

Endoluminal Therapies

Different endoluminal therapies have been developed in recent years, and many have disappeared because of either inefficiency or complications. Endoluminal therapies have been categorized in four different types: (1) fixation, (2) ablation, (3) injection, and (4) mucosal excision and suturing. Currently, only two techniques are widely available. Stretta is an anti-reflux device that consists of a four-channel radiofrequency-generating catheter delivering thermal energy, without reaching the ablation values into the muscularis propria within the oesophagus at four levels and cardia at two levels. A recent meta-analysis has shown that 49% of patients are off PPI following the procedure [37]. A long-term study has also revealed that the 5-year follow up results are consistent with the 10-year follow up results. The procedure certainly improves health-related quality of life and the pooled heartburn standardized score, reduces oesophageal acid exposure, and increases lower oesophageal sphincter basal pressure, although the last two features were not normalized. EsophyX (transoral incisionless fundoplication; TIF) is used to restore the angle of His by delivering multiple full thickness, nonabsorbable fasteners, and it creates a valve at the oesophagogastric junction [17].

Anti-reflux Surgery

Laparoscopic anti-reflux surgery is an effective long-term therapy option. It restores the mechanical barrier and improves LES pressure, decreases reflux episodes, and

improves symptoms and quality of life [38]. It can be safely performed with minimal perioperative morbidity and mortality. Shorter follow-up studies (<3 years) have observed better outcomes (90%) [39].

It is advisable that all NERD patients should be evaluated with oesophageal (high-resolution) manometry and 24 h pH (-impedance) or capsule pH monitoring study before surgery [10]. The best candidates are patients with good responses to PPIs and fewer functional gastrointestinal symptoms, such as bloating, belching or psychological co-morbidity. Patients with inadequate symptom control represent another group with difficulties, and they should be carefully evaluated before surgery for possible explanations for their failure to respond to medications. Typical symptoms respond better than atypical symptoms, and only patients with atypical symptoms should be carefully evaluated before the surgery and avoided if possible. Severe regurgitation (generally accompanied by hiatal hernia) and medication side-effects. Barrett's oesophagus and peptic structure can be treated surgically; however, there is no absolute indication in these groups.

Nissen was the most common choice between surgeons; however, partial fundoplication has attracted more attention in recent years because of the fewer postoperative complications, particularly dysphagia and bloating [38]. An interesting approach is to perform partial fundoplication in patients with preoperative major depression, as it may lead to better outcomes. Morbid obesity is a concern for higher surgery failures. For morbidly obese patients (BMI > 35 kg/m^2), gastric bypass should be the procedure of choice when treating GORD.

Summary of the Therapeutic Approach

Lifestyle changes, particularly weight loss, smoking cessation and possibly alcohol cessation, should be the first line approach in all cases. Strict dietary restrictions should be avoided because of the negative impact on quality of life. Many algorithms and approaches have been published. As shown in Fig. 2.3, as suggested by the Turkish consensus group, and the therapeutic approach was divided into three different categories: primary health care (first level), internists (second level) and gastroenterologists (third level) [40]. In the presence of the mild symptoms (less than three times a week, minimal impact on quality of life, short duration), on-demand therapy with any effective medication, such as antacids, alginate or antacid/alginate combination, H2 RA, and low dose of PPI, can be initiated. Moderate symptoms need a single dose of PPI; however, in cases of severe symptoms, a double dose of PPI with the combination of prokinetics or alginate is advisable. If upper gastrointestinal endoscopy is performed, the severity of findings should direct the dose, meaning that in cases of erosive oesophagitis A or B require a single dose, and C or D cases require a double dose of PPI. In patients who are unresponsive to the therapy, further diagnostic modalities, such as oesophageal manometry (high resolution if possible) and 24 h pH (impedance) monitoring, are advised [41]. While they are undergoing ambulatory pH-impedance recordings, patients should be carefully advised to describe their symptoms because some

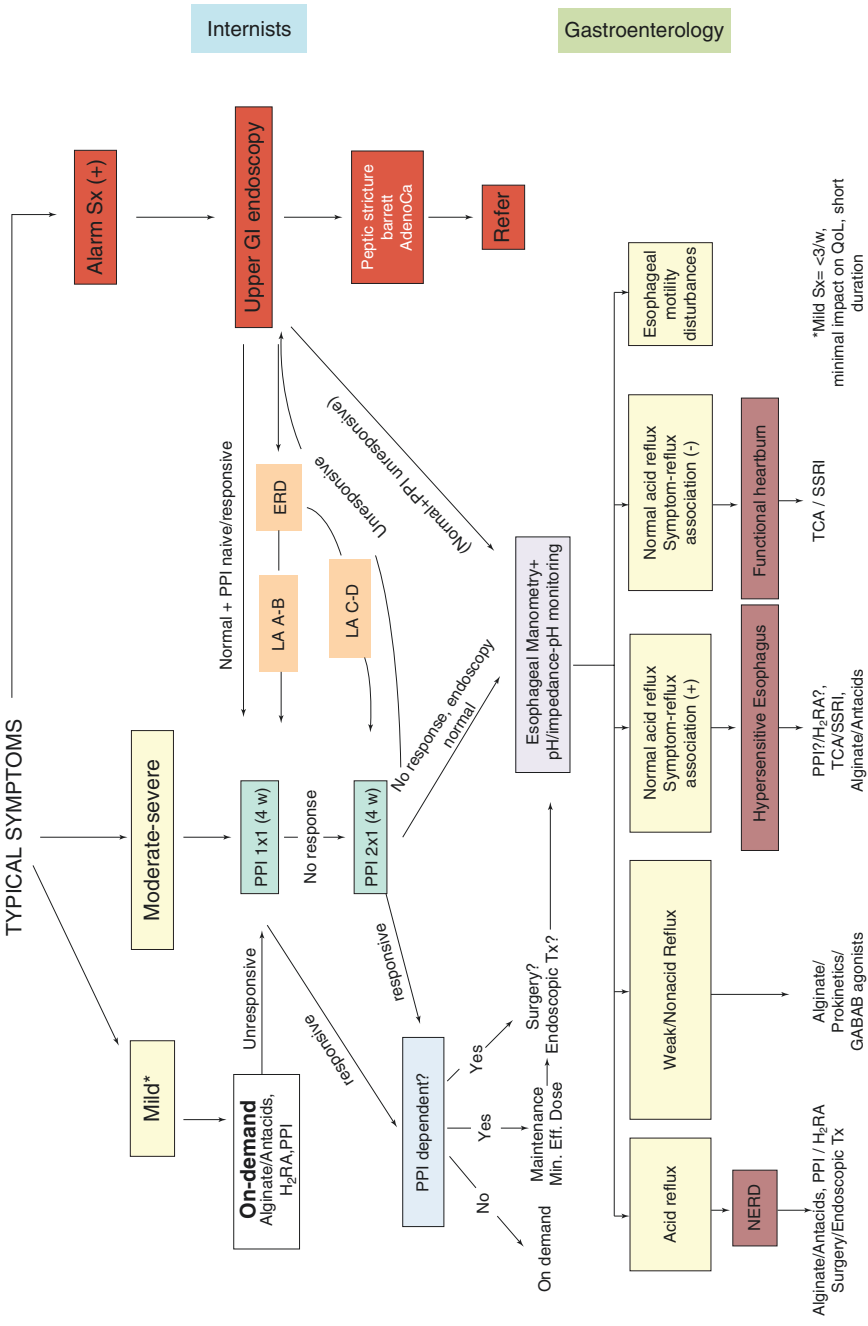

Fig. 2.3 Therapeutic algorithm inpatients with typical GERD symptoms [40]

GORD phenotypes, such as oesophageal hypersensitivity, are diagnosed based only on their reports. Those modalities are difficult to treat and generally do not response to classical GORD medications, especially anti-reflux surgery. They define more psychiatric co-morbidities compared to NERD and erosive patients. These subgroups and patients with functional heartburn need extensive evaluations of their psychiatric conditions, and tricyclics or SSRIs are commonly prescribed, as well as prokinetics.

The discontinuation of PPIs is possible, according to different studies, ranging from 14% to 64%, without deteriorating symptom control for a one-year period. Tapering may be a better approach than abrupt discontinuation [42].

Status of Newer Medications

Different new medications are currently under investigation. Here, some new achievements are summarized;

Improved Acid Suppression

In terms of better inhibition of gastric acid secretion, novel long-lasting PPIs and potassium-competitive acid blockers (P-CABs) are being developed.

Tenatoprazole and S-Tenatoprazole are imidazopyridine-based PPIs with a prolonged plasma half-life. It has been under development for years [43]. A Phase 2 study has been conducted in S Korea, and Phase 1 was conducted in the European Union and India.

Rabeprazole extended release 50 mg: Phase 3 has been completed and discontinued in some countries. It is registered in Turkey, and Phase 3 study is running.

Omeprazole+succinic acid (an acid pump activator VB 101; Vecam): A Phase 2 study was completed in 2011. Vecam, a combination of a PPI and succinic acid (an acid pump activator, VB101), is a drug that has meal-independent anti-secretory effect [44].

Ilaprazole (P-CAB) has been studied in phase III clinical trials, in which it failed to show superiority over esomeprazole in erosive oesophagitis and NERD [45]. It is registered in S. Korea, and at the Phase 2 level in China.

Vonoprazan is a new, potent and long-lasting acid inhibitory drug that exerts a direct and targeted effect on the parietal cell. It produces rapid, reversible, and long-lasting inhibition of the gastric H+, K+-ATPase. It has a reversible inhibitory effect on gastric acid secretion by competing with K+ on the luminal surface of the proton pump. The inhibitory effect acid secretion is independent of the secretory state of the H+, K+-ATPase. The efficacy of vonoprazan in patients with erosive oesophagitis was evaluated in a multicentre, randomized, double-blind, parallel-group, dose-ranging study. Vonoprazan at 5, 10, 20, and 40 mg doses was compared to PPI lansoprazole 30 mg for healing of EE at 4 and 8 weeks. The percent of EE healing at 4 weeks for vonoprazan was between 92.3% and 97.0%

and was dose-dependent, compared with 93.2% for lansoprazole [46]. It may play a potent role in patients' refractory to PPIs; however, it merits more and extensive research [47].

Helicobacter pylori and GORD

This issue is controversial, and deserves a special mention. The relationship between *Helicobacter pylori* and GORD is not clear. This topic is particularly important in countries with a high prevalence of HP. The Turkish GORD consensus group evaluated the literature, and the following statements were suggested [48];

- There is no clear association between HP and GORD [49, 50].
- The eradication of HP does not have any impact on either the appearance or exacerbation of GORD symptoms.
- Long-term PPI consumption does not have any impact on gastric atrophy in HP-positive cases [51, 52].
- The presence of HP might be protective for the development of Barrett oesophagus and oesophageal adeno cancer, particularly in cagA positive patients [53, 54].
- The screening and eradication of HP should be decided independently of the presence of GORD.

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