

Review article

Gastroesophageal Reflux Disease – An Update

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Summary

Gastroesophageal reflux disease (GERD) is a common disease and a considerable burden on healthcare resources. Definitions and terminology have been a source of confusion for GERD. The 'Montreal definition' is the first ever global consensus definition of GERD. The esophageal and extraesophageal syndromes are now considered the two constituent syndromes of GERD. The pathogenesis of gastroesophageal reflux is multi-factorial and a failure of the anti-reflux barrier allowing the stomach content to enter the esophagus is the target of interest. Heartburn and acid regurgitation are the typical symptoms of the disease, although some patients may have atypical manifestations of GERD. The long term complication of GERD includes esophageal stricture, Barrett's esophagus with consequent increase in the risk of esophageal adenocarcinoma. Diagnosis of GERD can usually be established on the basis of a careful history and physical examination. Detailed diagnostic studies are not necessary in a patient presenting with typical symptoms with no alarming features. Patients with alarming feature in addition to their GERD symptoms require prompt investigation and usually endoscopy is preferred. Treatment of GERD is directed at acid suppression through the use of lifestyle modifications and pharmacologic agents from over-the-counter (OTC) agents ranging from antacids to proton pump inhibitors (PPIs). New algorithm of treatment of GERD has also been proposed. Antireflux surgery, including open and laparoscopic, and newer endoscopic procedures are alternative modalities of treatment in case of failure of medical therapy.

Key words: Gastroesophageal reflux disease, Montreal definition, Esophageal syndrome, Extraesophageal syndrome, Heartburn, Regurgitation.

Gastroesophageal reflux disease (GERD)

Gastroesophageal reflux disease (GERD) is a common medical problem with a broad spectrum of symptoms and varying degrees of severity¹. The modern concept of reflux esophagitis dates back to 1935 when a landmark article in JAMA first suggested gastric secretions may cause the mucosal damage². Later in 1946 Allison identified the fundamental pathophysiological process and introduced the term 'reflux esophagitis'³.

Definition and Classification of GERD

The first ever global consensus definition of gastroesophageal reflux disease (GERD) is known as Montreal definition which defines the condition as "a condition which develops when the reflux of stomach

contents causes troublesome symptoms and/or complications"⁴.

The patients having GERD is broadly classified into two groups on the basis of endoscopy findings- having esophageal mucosal damage (erosive esophagitis and Barrett's esophagus) and no mucosal damage (endoscopy-negative reflux disease, symptomatic GERD, or non erosive reflux disease) (Box 1)⁵.

Heartburn and acid regurgitation are the archetypal symptoms of GERD and most

Box 1: GERD presentations⁵

Phenotypic presentations of GERD

1. Erosive esophagitis (20-30%)
2. Non erosive reflux disease (60-70%)
3. Barrett's esophagus (6-12%)

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patients with typical symptom of GERD can be treated empirically. Hence the term ‘heartburn dominant undiagnosed dyspepsia’ was coined to denote the group who have symptoms, referable to the esophagus or reduced quality of life attributable to gastroesophageal reflux, in the absence of any prior investigations⁶.

The Montreal definition did not use the term ‘nonerosive reflux disease’ but rather classified GERD into esophageal and extraesophageal syndromes. Esophageal GERD syndromes are categorized as those that are symptoms and other with esophageal injury while the extraesophageal syndromes are classified as of established or proposed association with GERD, acknowledging that while the evidence on hand is sufficient to link these syndromes to reflux, it is insufficient to establish causation⁴.

Epidemiology

Symptoms of GERD found to be very common, affecting up to 20% of the population in North America, 9% to 17% in Europe, 12% to 15% in Australia, and 2% to 5% in Asia once a week⁷. The study by El-Serag et al in 2004 reported that monthly prevalence of heartburn was 34.2%-40.6% in the United States⁸. Mishima et al reported that GERD was present in 17.9% of the Japanese people while Wong et al observed it 29.8% among

the Chinese population^{9,10}, Saberi-Firoozi et al reported prevalence to be 15.4% in Iran¹¹.

GERD is found to be equally prevalent among men and women. However, female preponderance (2:1 to 3:1) was observed in case of esophagitis and male in (10:1) Barrett’s metaplasia¹². Pregnancy is associated with the highest incidence of GERD with 48% to 79% of pregnant women complaining of heartburn¹³. The role of genetic factors was suggested by twin studies wherein heritability accounted for 31%-43% of the likelihood of reflux disease, which suggests both genetic and environmental factors play an important role in its pathogenesis^{14,15}. Regarding environmental factors there is sufficient evidence to support the relationship between being obese or overweight and GERD¹⁶. Among others factors dietary habits, the lack of physical activity and smoking frequently linked to be the risk factors for GERD. However, the exact pathogenic role of these factors is still debated^{17,18}.

Pathogenesis of GERD

Schematically, the esophagus, lower esophageal sphincter (LES), and stomach can be envisioned as a simple plumbing circuit. The esophagus functions as an antegrade pump, the LES as a valve, and the stomach as a reservoir. The

Table 1: The constituent syndromes of gastroesophageal reflux according to Montreal definition⁴

Esophageal Syndrome	
<i>Syndrome with symptoms</i>	<i>Syndromes with esophageal injury</i>
Typical reflux syndrome	Reflux esophagitis
Reflux chest pain syndrome	Reflux stricture
	Barrett esophagus
	Esophageal adenocarcinoma
Extraesophageal Syndrome	
<i>Established associations</i>	<i>Proposed associations</i>
Reflux cough syndrome	Pharyngitis
Reflux laryngitis syndrome	Sinusitis
Reflux asthma syndrome	Idiopathic pulmonary
Reflux dental	fibrosis
erosion syndrome	Recurrent otitis media

abnormalities that contribute to GERD can stem from any component of the system¹⁹.

The factors generally accepted as important for the development of gastroesophageal reflux disease (GERD) have been well documented (Box 2)²⁰⁻²². Despite the many factors that operate, four main fundamental factors stand out as most important: (1) gastric acid; (2) the structural integrity, function, and competence of the LES that either prevent or allow reflux; (3) the esophageal mucosal defense mechanisms that are primarily called into play when there is excess exposure of the mucosa to gastric acid; and (4) the sensory mechanisms that speak to symptoms²³.

A postprandial pocket of acid just below the gastro-esophageal junction has recently been described, and in patients with reflux, this acid pocket shows greater proximal extension, and is longer (Figure 1). As this acid pocket can persist for up to 2 hour postprandially and remains highly acidic compared with the body of the stomach, it is likely that gastric buffering from a meal creates a non-uniform environment with at least two acid layers; the lack of homogeneity of the stomach contents may

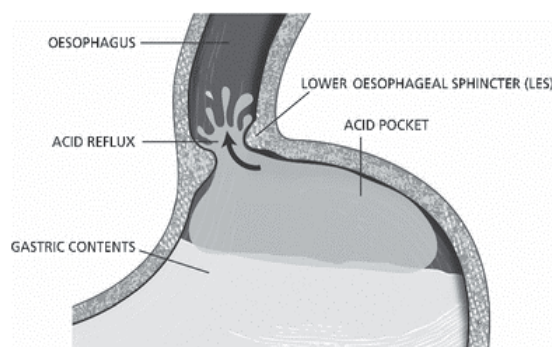


Figure 1: Postprandial acid pocket. This is a representation of the acid pocket; at this time the exact form and dimensions are to be determined²⁴

explain persistent acidic gastro-esophageal reflux after a meal²⁴.

The role of duodenogastroesophageal reflux still remains controversial. Patients with both acid and duodenal content in the esophagus had a high frequency (67%) of and more severe esophagitis, and duodenogastric reflux is more common in GERD patients with stricture or Barrett's esophagus. Hiatus hernia frequently accompanies GERD and may contribute to prolonged gastric content exposure time following reflux. Patients with GERD do not necessarily have a hiatus hernia and, conversely, those with hiatus hernia do not invariably have GERD²³.

Box 2: Factors important to the development of gastroesophageal reflux disease (GERD)

- Gastric acid and other refluxed materials (e.g., bile, pepsin, enzymes, others)
- Structural and physiologic antireflux mechanisms at the gastroesophageal junction (LES, diaphragm, hiatus hernia, phreno-esophageal ligament)
- Transient lower esophageal sphincter relaxations (TLESR)
- Esophageal clearance mechanisms (esophageal motility, gravity, salivary bicarbonate)
- Mucosal integrity and defense mechanisms
- Ingested irritants (e.g., nonsteroidal antiinflammatory drugs, certain antibiotics)
- Ingested substances and drugs that affect esophageal, LES, or gastric motility (e.g. alcohol, medications)
- Sensory mechanisms
- Other (delayed gastric emptying, inflammation-esophagitis, genetics, psycho-behavioral factors)

Table 2: Extraesophageal Symptoms and Signs Associated with Gastroesophageal Reflux Disease²⁷

<i>Ear, Nose and Throat</i>	<i>Pulmonary</i>	<i>Others</i>
Hoarseness	Asthma	Noncardiac chest pain
Cough	Bronchitis	Dental erosion
Globus	Bronchiectasis	Sleep apnea
Pharyngitis	Aspiration pneumonia	
Otitis	Idiopathic pulmonary	
Laryngitis	fibrosis	
Sinusitis		
Vocal cord granuloma		
Subglottic stenosis		
Laryngeal cancer		

Clinical presentation

The most common symptoms of GERD include heartburn or pyrosis, regurgitation, and dysphagia. Heartburn, defined as a burning sensation in the retrosternal area, has a specificity of 89% and positive predictive value of 81% for GERD. Regurgitation, defined as the sensation of gastric refluxate into the mouth or hypopharynx, has a specificity of 95% and positive predictive value of 57% for GERD. The combination of heartburn and regurgitation has an accuracy of greater than 90% for the diagnosis of GERD²⁵. Increasing information is being gained through recent evidence regarding the “extraesophageal” presentations of this disease. These patients frequently do not complain of associated heartburn and regurgitation, leading to another synonym for this syndrome—the “atypical” presentations of GERD²⁶. As many as 80% of patients with GERD may have at least one extraesophageal symptom²⁴. The common atypical symptoms are asthma like symptom, chest pain, cough, laryngitis and sinusitis (Table 2).

Complications of GERD**Strictures**

Peptic strictures represent severe end stages of reflux disease. Not only do peptic strictures develop in 4% to 20% of patients with reflux esophagitis, but as many as 25% to 50% of stricture cases have a

concomitant columnar metaplasia of the squamous epithelium (Barrett's esophagus)²².

Barrett Esophagus (BE)

The most serious histologic consequence of GERD is Barrett's metaplasia. As a consequence of clinical and epidemiological evidence supporting the association between BE and esophageal adenocarcinoma.

BE is considered a precancerous lesion and accurate diagnosis of BE is crucial²⁸⁻³⁰. Patients with long-standing reflux symptoms are at risk for Barrett's esophagus. Microscopically, Barrett's is characterized by replacement of the normal squamous epithelium of the esophagus with a specialized columnar epithelium, known as intestinal metaplasia²⁵. On endoscopic examination morphologically BE is a tongue-like extension of salmon-colored mucosa from the gastroesophageal junction³¹. Prevalence of BE in Western countries found to be varied from 6.3-13.6% in patients with GERD³².

Hemorrhage

Whereas most patients with reflux esophagitis have little or no evidence of gastrointestinal bleeding, those with esophageal erosions and ulcers may develop chronic bleeding and iron deficiency anemia³³.

Perforation

Esophageal perforation is a rare complication of GERD. Like major hemorrhage, it usually develops as a consequence of an esophageal ulcer which results in mediastinitis³³.

Natural history of GERD

Most GERD patients do not seek medical attention and usually self-medicated. Two potential paradigms for the natural history of GERD exist. GERD is generally viewed as a progressive disease such that, in the absence of effective intervention, patient with nonerosive disease becomes tomorrow's patient with erosive disease and would become a candidate for the development of Barrett's esophagus. This "spectrum of disease" approach has been contrasted with the view that GERD may be a disease with phenotypically discreet "categories," such as nonerosive disease, erosive esophagitis, and Barrett's esophagus. In this view, conversion from one disease manifestation to another is distinctly unusual, and subjects generally stay in their initial category. Available, albeit limited, data suggest that while subjects with GERD may sometimes progress from nonerosive disease to erosive esophagitis (making it not a strictly categorical disease), the reported rates of progression are relatively low over a 20-year period. In patients in whom stricture, Barrett's metaplasia, and adenocarcinoma were excluded in the setting of a healed mucosa at index endoscopy, the likelihood of these developing within a 7-year follow-up period is on the order of 1.9%, 0.0%, and 0.1%, respectively³⁴.

Differential diagnosis

Symptoms associated with GERD may be mimicked by coronary artery disease, gallbladder disease, gastric or esophageal malignancy, peptic ulcer disease, and eosinophilic, infectious, or caustic esophagitis, atypical cases of achalasia,

distal esophageal spasm or functional heartburn^{34,35}.

Diagnosis of GERD

It is neither practical nor necessary to embark on a diagnostic evaluation of every patient who experience only heartburn. The primary goal of therapy is symptomatic relief. A diagnostic test for esophageal GERD syndromes is invoked in 3 broad scenarios: (1) avert misdiagnosis; (2) identify complications of reflux disease; and (3) evaluation of empirical treatment failures³⁴.

Symptom-based diagnosis of GERD

The Montreal definition recognizes that GERD can be diagnosed in primary care on the basis of symptoms alone without additional diagnostic testing^{4,36,37}. A well-taken history is essential in establishing the diagnosis of GERD. Symptoms of classic burning in the chest, with sour or bitter taste, and acid regurgitation have been shown to correctly identify GERD with a sensitivity of 89% and specificity of 94%. However, symptom frequency, duration and severity are equally distributed among patients with varying grades of esophagitis and Barrett's esophagus and cannot be used reliably to diagnose complications of GERD³⁸.

Empiric/therapeutic trial

Diagnostic modalities cannot reliably exclude GERD even if they are negative. Therefore an empiric trial may be the most expeditious way in which to diagnose GERD in those with classic symptoms and who do not have symptoms suggestive of complications (e.g., carcinoma, stricture). Empiric therapy should be tried for two weeks for patients with typical GERD symptoms. Treatment can be initiated with standard dosage of either an H2 receptor antagonist (H2RA) twice daily (BID) or on demand; or a Proton pump inhibitor (PPI), with drug selection depending on clinical presentation and appropriate cost

effectiveness and the end point of complete symptom relief. If symptom relief is not adequate and H2RA twice daily was initially used, then PPI daily should be used. If PPI daily was initially used, then increase it to maximum dose PPI daily or BID (30-60 minutes prior to first and last meals)³⁸.

Endoscopy

Endoscopy at presentation should be considered in patients who have symptoms suggestive of complicated disease or those at risk for BE^{39,40} (Box 3). Failure to respond to appropriate antisecretory medical therapy should prompt evaluation with EGD. Endoscopy is the primary technique for evaluating mucosal integrity, esophageal stricture formation, and Barrett's esophagus with a sensitivity of 50% and specificity of 95%. Endoscopic evidence of esophagitis occurs in less than 50% of people who have experienced heartburn greater than twice a week over a six month time period³⁸. Esophagitis is best defined by the LA classification system and identifies the degree to which mucosal breaks (erosions or ulcerations) occur, graded in severity from A to D, with D being the most severe⁴¹. Biopsy is indicated in defining Barrett's esophagus⁴¹.

Box 3: Indications for endoscopy and further investigations

Alarm Features for GERD

- Dysphagia (solid food, progressive),
- Odynophagia (painful swallowing)
- choking, chest pain
- Bleeding/anemia
- Weight loss
- Persistent vomiting

Other Indications for Further Investigation

- GERD symptoms that could be cardiac in origin.
- Respiratory symptoms secondary to reflux

Ambulatory PH monitoring

Although no gold standard test exists for the diagnosis of GERD, ambulatory pH monitoring is accepted as the standard with a sensitivity of 85% and specificity of 95%³⁸. Patients with endoscopic-negative GERD and who do not respond to medications are best evaluated by ambulatory pH monitoring. The purpose for pH probe must be defined before proceeding: is it to diagnose GERD or to determine the adequacy of therapy. The test should be performed off therapy if the diagnosis is under question. The test should be performed on therapy if one is trying to determine the adequacy of treatment. Recent advances in “wireless” pH radiotelemetry capsule eliminate the need for the uncomfortable naso-esophageal tube, and increases diagnostic yield by allowing for longer monitoring. Ambulatory pH monitoring is based upon the amount of time the intraesophageal pH is less than 4, with normal defined as less than 4% over a 24-hour period^{34,38}.

Other diagnostic modalities

Esophageal manometry can be used to evaluate patients with a suspected esophageal GERD syndrome who have not responded to an empirical trial of twice-daily PPI therapy and have normal findings on endoscopy. Manometry will serve to localize the lower esophageal sphincter for potential subsequent pH monitoring, to evaluate peristaltic function preoperatively, and to diagnose subtle presentations of the major motor disorders. Evolving information suggests that high-resolution manometry has superior sensitivity to conventional manometry in recognizing atypical cases of achalasia and distal esophageal spasm^{34,40}.

Esophageal capsule endoscopy in patients with suspected GERD and other esophageal disorders is feasible and safe, and could be also an alternative procedure in those patients refusing upper endoscopy⁴².

Box 4: Suggested Lifestyle Modifications for Patients with GERD⁴⁰

- Avoid large meals
- Avoid acidic foods (citrus- and tomato-based products), alcohol, caffeinated beverages, chocolate, onions, garlic, and peppermint
- Decrease dietary fat intake
- Avoid lying down within three to four hours after a meal
- Avoid medications that may potentiate GERD symptoms, including calcium channel blockers, beta agonists, alpha-adrenergic agonists, theophylline, nitrates, and some sedatives
- Elevate the head of the bed 10 to 20 cm (4 to 8 inches)
- Avoid wearing clothing that is tight around the waist
- Lose weight
- Stop smoking

Treatment of GERD***Lifestyle modifications***

Based on expert opinion, lifestyle modifications should be initiated and continued throughout the course of therapy in patients with a history of typical uncomplicated GERD⁴³. Weight loss should be advised for overweight or obese patients with esophageal GERD syndromes and elevation of the head of the bed for patients who are troubled with heartburn or regurgitation when recumbent. Other lifestyle modifications including, but not limited to, avoiding late meals, avoiding specific foods, or avoidance of specific activities should be tailored to the circumstances of the individual cases^{34,38}. Although there is little supporting evidence, it is considered reasonable to educate patients about various factors that may precipitate reflux⁴⁴.

Antacids and alginates

These acid suppressants are appropriate, initial patient-directed therapy for GERD. Antacids and combined antacid/alginic acid have been shown to be more effective than placebo in the relief of daytime GERD symptoms.^{34,38,40}

Antisecretory Therapies

Anti-secretory drugs are recommended strongly for the treatment of patients with esophageal GERD syndromes (healing esophagitis and symptomatic relief). A

short course or as-needed use of antisecretory drugs should be used in patients with a symptomatic esophageal syndrome without esophagitis when symptom control is the primary objective. For a short course of therapy, PPIs are more effective than H2RAs, which are more effective than placebo^{34,45}. Twice-daily PPI therapy is recommended for patients with an esophageal syndrome with an inadequate symptom response to once-daily PPI therapy. The most common side effects of PPIs are headache, diarrhea, constipation, and abdominal pain. Switching among alternative PPI drugs or to a lower dose can usually circumvent these side effects. As for the issue of onset of action, this primarily pertains to on-demand therapy. If a patient intends to take a drug only in response to symptoms, then it should be a rapidly acting drug. The most rapidly acting agents are antacids, the efficacy of which can be sustained by combining them with an H2RA or a PPI³⁴.

Prokinetic or promotility agents

Drugs such as cisapride, metoclopramide and domperidone have been tried in the treatment of GERD. These agents have been proposed to increase peristalsis and LES tone. Cisapride is the only prokinetic agent that has shown clinical efficacy⁴⁶; however, it is no longer available on the market due to concerns about prolongation of QT interval, ventricular tachycardia and death. Due to the paucity of clinically

relevant data, these agents are not recommended alone or in combination with anti-secretory agents for the long-term maintenance treatment of GERD^{6,47,48}.

Treatment of patients with extraesophageal GERD Syndrome

Twice-daily PPI therapy is recommended as an empirical trial for patients with suspected reflux chest pain syndrome after a cardiac etiology has been carefully considered. Acute or maintenance therapy with once- or twice-daily PPIs (or H2RAs) is recommended for patients with a suspected extraesophageal GERD syndrome (laryngitis, asthma) with a concomitant esophageal GERD syndrome³⁴.

Maintenance treatment in GERD³⁸

The goal of maintenance therapy is to have a symptom free individual with no esophagitis. Chronic acid suppression will be required for adequate symptom control in the majority of subjects with GERD symptoms severe enough to warrant initial PPI therapy. While many subjects may tolerate dose reduction of their PPI and maintain adequate symptom control, the likelihood of long-term spontaneous remission of disease is low. Beyond recurrence of symptoms and/or erosive disease, the risks associated with cessation of therapy, including the possible development of Barrett's esophagus, appear minimal.

Options in maintenance regimens include: step-up therapy (starting less potent agents and moving up for treatment response), step-down therapy (using potent acid suppression initially with decreasing dose or less potent agents to tailor to the individuals response), on demand (patient-directed) therapy, or surgery. All options have the goal of complete symptom relief.

Step-up therapy: When beginning step-up therapy, no more than 2 weeks is needed to determine if a dosage of medication will be effective. If a patient does not respond to

an H2 receptor antagonist within 2 weeks, the patient should be switched to a proton pump inhibitor, again emphasizing it be used 30 minutes to 1 hour prior to meals so that the PPI has time to interact with an activated pump. If the patient does not respond to this program, a double dose program (BID; 30 minutes before breakfast and 30 minutes before dinner) may be effective in reducing symptoms. If the patient does not respond to this program, the patient is likely not to have reflux as a source of their symptoms and diagnostic testing would be appropriate.

Step-down therapy: Once symptoms are controlled after step-up therapy, step-down therapy commences with the patient taking a PPI for 8 weeks, followed by an H2RA if GERD symptoms were adequately controlled with a PPI, then stepping down further to on-demand use of antacids if the patient was asymptomatic while taking an H2RA. The majority of patients who take more than a single daily dose of a PPI and who experience relief of symptoms can be successfully stepped down to single-dose therapy without a recurrence of reflux symptoms. However, a small percentage of patients with refractory GERD will need long-term therapy with higher doses of a PPI to control symptoms.

On demand therapy

Treatment can be initiated with standard dosage of either a PPI daily or an H2RA twice daily on demand (patient directed therapy). Drug selection depends on clinical presentation, cost-effectiveness, and end point of appropriate symptom relief.

Role of Surgical treatment

Consideration of antireflux surgery must be individualized⁴³. Patients who are well maintained on medical therapy have more to lose than to gain and should not be offered surgery⁴⁹. Surgery may be recommended^{6,34} in the following situations:

1. When a patient with an esophageal GERD syndrome is responsive to, but intolerant of, acid suppressive therapy, or
2. has persistent troublesome symptoms, especially troublesome regurgitation, despite PPI therapy
3. Poor compliance (for example, due to medication costs)
4. Presence of a large hiatus hernia

The potential benefits of antireflux surgery should be weighed against the deleterious effect of new symptoms consequent from surgery, particularly dysphagia, flatulence, an inability to belch, and post surgery bowel symptoms³⁴.

Newer endoscopic treatments

The endoluminal treatment of GERD is evolving and may have the potential to decrease the need for long-term antisecretory medications in selected patients³⁴. A variety of endoscopic techniques for the treatment of GERD are currently available, including the delivery of radiofrequency energy to the gastroesophageal junction and suture plication of the proximal fundic folds, but there are no longer any devices that require injection of bulking agents or implantation of a bioprosthesis into the LES zone. Most studies of endoscopic therapy have only limited follow-up information, and data suggest that some of these techniques, in their current position, are not durable⁵⁰.

Frequently reported complications for endoscopic treatments, intraoperatively or within 30 days after the procedure, included chest or retrosternal pain, gastrointestinal injury, bleeding, and short-term dysphagia⁵¹.

Updated Treatment Algorithm

An updated treatment algorithm for the management of reflux disorders was suggested by an expert panel in 2006 (Table 3). This algorithm can be followed by patients and pharmacists when choosing

OTC medications, PCPs and gastroenterologists in a secondary care setting²⁴.

The algorithm is separated into three distinct therapeutic levels (self-care, primary care, and secondary care), with clear recommendations being provided at each level of care. A careful history and physical evaluation is essential, and consideration given as to whether the symptoms warrant an alternative diagnosis. Any alarm symptoms should be immediately referred for specialist investigation²⁴.

Prospective pharmacotherapeutic agents for GERD⁵²

New proton pump inhibitor isomers

Isomers of proton pump inhibitors e.g. S-isomer of omeprazole. S-pantoprazole and dexrabeprazole, are new isomers that offer therapeutic advantages as compared to racemic pantoprazole and racemic rabeprazole respectively.

New proton pump inhibitors

Tenaprazole (Tu-199) is a novel chemical compound which also belongs to the proton pump inhibitor class. Unlike other PPIs, tenaprazole is characterized by substantially prolonged half-life (7 hours).

Potassium competitive acid blockers

Potassium-competitive acid blockers (P-CABs) represent a new class of drugs acting through a reversible binding mechanism different from the PPIs. In pharmacological studies, they have shown a fast onset of action (within 30 minutes of drug administration) with a maximum effect obtained after the first dose, whereas classical PPIs needs several days to reach their steady-state effect.

Table 3: Updated Treatment Algorithm of GERD²⁴

<i>Self care</i>			
Episodic symptoms		Troublesome symptoms	Alarm symptoms
OTC therapy (antacids, alginates, PPI, H2RA) ↓ Success- Continue therapy Failure- Consultation with primary care physician		Consultation with primary care physician	Consultation with primary care physician
<i>Primary Care</i>			
(Evaluate, consider personal and family history, drug history, Compliance and rule out other Conditions, e.g. cardiac)			
Presumably GERD Reassurance and/or optimize OTC and/or PPI+ adjuvant therapy for 4-8 weeks		Consider alternate diagnosis	Alarm symptoms Consultation with secondary care physician
↓			
1. Success	2. Failure		
Step down and stop. In case of relapse restart on lowest effective dose ↓ a. Success-Continue, aim for lowest effective dose b. Failure ¹ →→2	BID PPI +/- adjuvant therapy 4 weeks and review ↓ 1a. ←←← Success Failure ¹ →Consider referral to specialist		
<i>Secondary Care</i>			
(Evaluate, consider personal and family history, drug history, Compliance and rule out other Conditions, e.g. cardiac)			
Presumably GERD Consider optimizing therapy or investigation (endoscopy+/- additional investigation)			Consider alternate diagnosis
↓			
Alternative diagnosis	NERD/GERD-AB	GERD-CD	Barrett's
	PPI+/- adjuvant therapy for 4-8 weeks ↓ Success- on demand/maintenance PPI 3-6 months Failure- BID PPI +/- adjuvant therapy 8-12 weeks ↓ Success- long term maintenance PPI Failure ¹ - re-evaluation/refractory	PPI+/- adjuvant therapy for 8 weeks ↓ Success- Long-term maintenance PPI +/- adjuvant Failure- BID PPI +/- adjuvant therapy 8-12 weeks ↓ Success- long term maintenance PPI Failure ¹ - re-evaluation/refractory	Long-term PPI +/- adjuvant

¹In cases of failure always consider alternate diagnosis.

Adjuvant therapy: corresponds to antacids or alginate-antacids.

Alarm symptoms: dysphagia, bleeding, anemia, weight loss, choking, chest pain, frequent vomiting.

Failure: unresponsiveness to treatment, unsatisfactory symptom relief, too frequent use of treatment (over-the-counter, self-care level).

Intermittent: defined as ≤1/week. Troublesome symptoms: defined as ≥2/week

Lowest effective dose: lowest dose capable of providing symptom relief, which may range from no drug to single-dose proton pump inhibitor (PPI).

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