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Edited by Ali Ibrahim Yahya

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Meet the editor

Ali Ibrahim Yahya is the Director of General Surgical Specialty at the Libyan Postgraduate Board. He is also an examiner for Libyan medical schools and the Libyan Postgraduate Board. He received his Diploma in Laparoscopic Surgery in Strasbourg. He was the Dean of Zliten Medical School from 2013 to 2018 and tutor of the High Surgical Skill Course at the Royal College of Surgeons in Edinburgh. He is an editor and reviewer of national and international surgical journals and has presented 45 scientific papers in congresses locally and internationally. He has also published 15 scientific surgical papers in international surgical journals, four chapters in books and short notes in books on pancreatitis.

Contents

Preface

Writing this book on gastroesophageal reflux disease is the result of a long journey of work. When I left the UK 27 years ago and after I received a fellowship from the Royal College of Surgeons of Edinburgh, I did my surgical training and joined the surgery department at Zliten University Hospital as young surgeon. At that time there were no surgeons performing endoscopy at the hospital and because I was encountering patients with upper gastrointestinal bleeding I had to perform elective and emergency upper gastrointestinal endoscopy. During this time in surgical endoscopy I faced many patients who came for diagnosis with symptoms typical of gastroesophageal reflux disease. Some of these patients were treated with medicine and others with surgery where reflux only, or reflux with hiatus hernia was diagnosed. From that day to this the idea of publishing a book on gastroesophageal reflux disease was born, and has now come to reality. Since gastroesophageal reflux disease is a common benign clinical problem in most countries and most practicing doctors will face patients who will need diagnosis and treatment. This book will be useful for resident upper gastrointestinal tract surgeons and gastroenterologists, as well as general practitioners. The book discusses the increase in gastric acid secretion and reactive oxygen species in the pathophysiology of reflux esophagitis, as well as the treatment and diagnosis of refractory gastroesophageal reflux disease. Gastroesophageal reflux disease can be seen in any age group and in the book there is a chapter that discusses the presentation, diagnosis and treatment of the disease in children. Finally, I would like to thank all authors for their contributions and for distributing their valuable knowledge to readers all over the world. Great thanks must go to Dolores Kuzelj who shared our long journey and put all her efforts into making this book a reality. My thanks also go to the IntechOpen publisher staff.

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Chapter 1

Introductory Chapter: Gastroesophageal Reflux Disease

Ali I. Yahya

1. Introduction

Gastroesophageal reflux disease (GERD) occurs frequently in developed countries. The number of cases, in fact, is increasing in the Middle East countries. In western countries, its occurrence ranges from 10 to 20% of the population who may present with typical or atypical symptoms or with complications. Although GERD was described by Asher Winkelstein, an American gastroenterologist, in 1935, it had appeared among patients earlier than that time. Nowadays, cases of GERD are common among obese individuals, patients with gallbladder disease, and those individuals under stress. It has also become a common clinical problem that commonly affects young adults, both male and female, of 40 years old.

2. History of GERD

1855—Bowditch Rokitansky reported that esophagitis was due to gastroesophageal reflux. Allison and Barrett found the association between hiatus hernia and gastroesophageal reflux.

1828—Charles Millard in Paris noticed the first case of esophagitis in child.

1879—Heinrich Quincke reported that ulceration in the esophagus was due to gastroesophageal reflux.

1906—Tilston described the typical symptoms of esophagitis.

1920—Joseph Sheehan described the endoscopic findings of esophagitis.

1921—Porter Vinson noted the association between stricture and esophagitis.

1934—Hampel introduced the term peptic esophagitis.

1956—Rudolf Nissen performed a successful fundoplication for patient, who suffered from GERD, with hiatus hernia. Patient was cured from the complaint.

3. Anatomy and Physiology

At the lower end of the esophagus is a sphincter which is formed by a change in the muscles of the esophagus. This sphincter controls the flow of esophageal contents to the stomach. Different factors related to the anatomy and physiology of the sphincter prevent the reflux of gastric contents into the esophagus. Among these factors include the following:

1. High pressure zone: Pressure at the lower esophageal sphincter area is high than stomach pressure (gastric pressure is +4 to +6, at the lower esophageal sphincter is +24 mmgh, and in the thoracic esophagus is −6). Because of the high

pressure at the sphincter, reflux is prevented. There are specific factors which will increase the tone of the sphincter, as well as factors like taking fatty meals, chocolate, smoking, and oral contraceptives that will reduce the tone of the sphincter.

2. The length of the lower esophageal sphincter is 3 cm which is divided into abdominal part and thoracic part. If the abdominal part is less than 2 cm, patient will get reflux. Other factors like change of mucosa, the muscular coat of the stomach which will have oblique muscles in addition to the other two types of circular and longitudinal, crural effect and angulation of the esophagus to the stomach which is called Angle of His are not important in the prevention of the gastroesophageal reflux.

3. Other factors that increase the effect of acid on the esophagus. Among these factors include the delayed gastric emptying. The increasing amount of the food in the stomach will lead to absorption of the sphincter and will increase the reflux. Reduced mucus and reduced saliva will lead to reduced bicarbonate which will reduce the effect of the acid refluxate.

4. Clinical presentation of gastroesophageal reflux disease

GERD appears with typical symptoms or rarely by atypical symptoms, which resemble cardiac symptoms and have been called cardiac symptoms.

4.1 Typical symptoms

Typical symptoms which appear among 70% of patients include the following:

1. Retrosternal pain (i.e., heart burn): It is the most common symptom which will be more manifested when patient is lying down or after meal and is seen among 80% of patients.

2. Regurgitation: It is a symptom observed when gastric or esophageal content comes in the mouth effortlessly. Regurgitation of gastric content will reach tracheobronchial tree and will induce hoarseness of voice which is usually experienced in the morning. This hoarseness could be due to reflux of gastric content into the larynx or due to vagal irritation and will induce reflex spasm of the vocal cords. This symptom is seen among 50% of patients [1–6].

3. Dysphagia: This is observed among 20% of patients with gastroesophageal reflux disease.

Some rare presenting complaints, with rate of occurrence among patients, are as follows:

1. Abdominal pain: 30%

2. Belching: 30%

3. Coughing: 20%

4. Wheezing: 10%

4.2 Atypical symptoms

Atypical symptoms are those where the patient will present with symptoms not related to gastrointestinal system: coughing, wheezing, recurrent pharyngitis, laryngitis, and chest pain. Its acute onset may resemble acute myocardial infarction.

Patient may present with complicated gastroesophageal reflux disease— some symptoms include the following: stricture, Barrett esophagus, lung damage in the form of pneumonia, and lung fibrosis if condition goes chronic.

5. Investigations

1. **Upper gastrointestinal endoscopy:** Upper gastrointestinal endoscopy is very important to exclude other serious disease which may mimic reflux, like tumors [7]. Upper gastrointestinal endoscopy can confirm hiatus hernia (**Figure 1**). Esophagitis will be experienced by 50% of patients with GERD. It can also diagnose Barrett esophagus and esophageal peptic stricture (**Figure 2**).

2. **Contrast barium study:** It is applied to detect hiatal hernia and esophageal stricture [8]. Barium contrast study can show hiatus hernia which can be small or large sac (**Figures 3–5**).

3. **PH monitoring:** 24 pH monitoring is very important in atypical presentation of gastroesophageal reflux disease [9, 10]. It can confirm or exclude the disease, with a diagnostic rate of 70–90%. It is not indicated in patients with esophagitis.

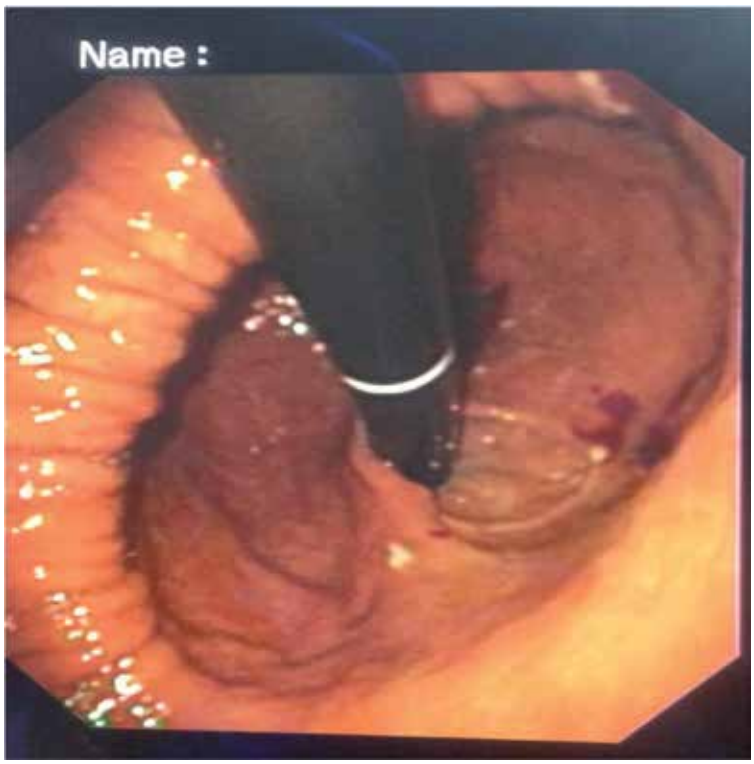

Figure 1.
The use of upper gastrointestinal endoscopy showing hiatus hernia in patient with GERD.

4. **Gastroesophageal scintigraphy:** Where drink like orange juice or milk is labeled with technetium and is used to study reflux, this test is rarely used for diagnosis of GERD. It is used in small children where we can study the reflexate to the lung, and the test is easy in small babies in comparison to other invasive tests. Gastroesophageal scintigraphy is used for patient who presents with atypical reflux symptoms like recurrent upper respiratory symptoms.

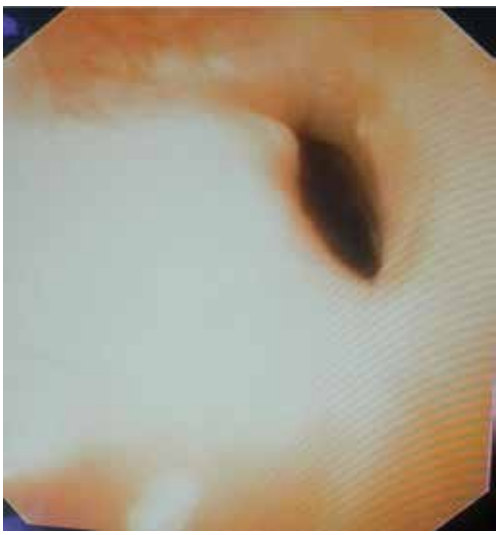

Figure 2.
The use of upper gastrointestinal endoscopy showing peptic stricture.

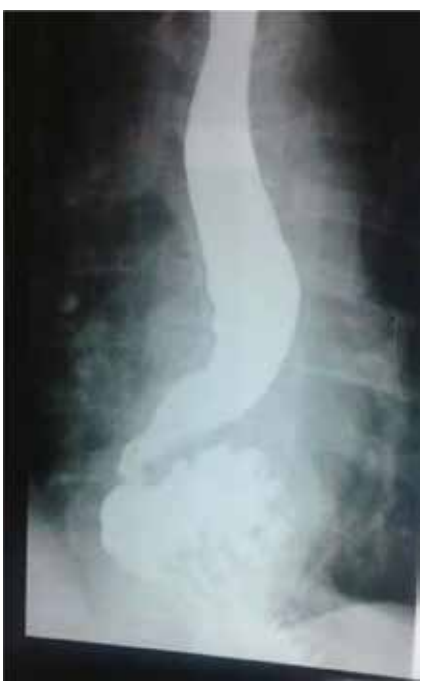

Figure 3.
Barium metal showing hiatus hernia.

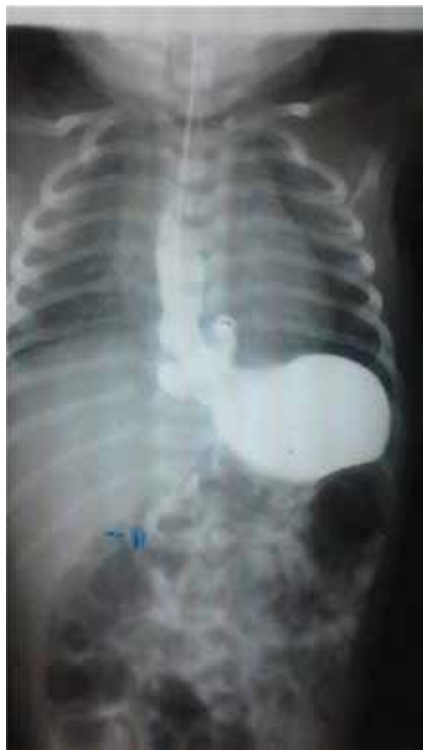

Figure 4.
Barium metal showing child hiatus hernia.

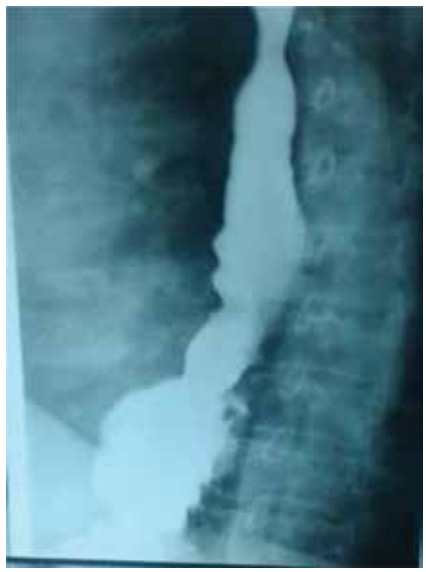

Figure 5.
Hiatus hernia with esophageal spasm.

5. **Multichannel impedance pH monitoring:** It is a gold standard technique for diagnosis of GERD; it is more superior and more sensitive in diagnosing GERD than usual pH monitoring.

6. **Manometry:** It is a very important investigation to exclude motility disorders like achalasia and is indicated in patient who presents with atypical symptoms of gastroesophageal reflux disease. High-resolution manometry is more sensitive and superior than ordinary manometry in diagnosing esophageal motility disorders.

6. Treatment

Reasons for treating GERD:

1. Heart burn is a troubling symptom and affects patient life.

2. Complications of GERD may cause esophagitis which will result to bleeding. Predisposition to Barrett esophagus that may turn to malignancy is 40–60 times seen in patient with reflux esophagitis-induced Barrett [11–13].

6.1 Nonsurgical treatment of gastroesophageal reflux disease

1. Change of lifestyle

    a. Avoid having late meals, heavy meals, spicy or fatty meals, drinking alcohol, and smoking.

    b. Reduce weight; avoid tight clothes around the waist.

    c. Avoid drugs which reduce the tone of sphincter.

2. Medical

Medical treatment where drugs are used to neutralize the effect of the reflux on esophageal mucosa:

a. Antacids: Drugs that will neutralize the acid effect include the following—calcium, aluminum, and magnesium compounds. These are best taken after meals. Their effect is brief; and once they get emptied from the stomach, the symptoms may come back. These need to be given on an hour base to neutralize the acid effect.

b. Histamine antagonists: There are receptors on the acid-producing cells which are stimulated by histamine to produce acid. These receptors are blocked by histamine-blocking drugs which act on H2 receptors. These drugs are best taken before meals. These include cimetidine which can be given 400–800 mg daily, ranitidine given 150 mg twice daily, and famotidine given 20–40 mg twice daily.

c. Proton-pump inhibitors: These include omeprazole, esomeprazole, lansoprazole, pantoprazole, and rabeprazole. Their dosages range from 20 to 40 mg daily. PPI will cure the esophagitis up to 90%; 80% will recur within 1 year if treatment is stopped [14–17].

7. Surgery

Indication of surgery:

1. Failure of medical treatment.

2. Development of complications of the drugs.

3. Association with large hiatal hernia.

4. Atypical presentation with positive 24 h pH records.

5. Patients do not like to take drug for long life to control the symptoms.

7.1 Surgery for GERD

It can be done by lengthening the lower esophageal sphincter to create valve-like action to prevent refluxing of gastric contents in the esophagus. Procedure is done by wrapping the stomach around the lower esophagus [18–20], either full wrap of 360° (which is named after Nissen) or partial wrap of 270°, either done posteriorly or anteriorly.

Fundoplication was previously performed by open surgery. Nowadays, most operations are done laparoscopically (**Figures 6** and 7), with excellent outcome on short-term and long-term follow-ups.

Patient will stop taking the drugs. All patients should be seen by gastroenterologist, ENT specialist, and surgeons before surgery, especially for those patients who come with atypical symptoms of GERD.

For many years, open surgery has been used for hiatus hernia but was rarely applied for GERD without hernia. Many operations can be done, either abdominal approach or thoracic approach. The common operation is the Nissen fundoplication which has been used since 1950, with a success rate of 80–90%. Its complication rate ranges from 10 to 15% and includes difficulty in swallowing and flatulence which may go for some time than ease off.

7.2 Endoluminal surgery (NOTES)

It is also called incisionless surgery. Endoscopic treatment of GERD is still under investigation:

1. Natural orifices transendoscopic surgery [21–25]

2. Endoscopic augmentation of lower esophageal sphincter, either by radio frequency application or injection of ethylene vinyl alcohol in the region of the lower esophageal sphincter [26–30].

7.3 Esophageal magnet ring

It is a new technique where there is no need to make wrapping around the lower esophagus by the stomach. This is a magnet ring fixed around the lower esophagus [31, 32]. It is not widely used and still under trial where magnet ring is fixed laparoscopically around the esophageal sphincter. It moves out once food comes in, and it comes back when the food enters the stomach. It has benefit

over Nissen fundoplication. The patient can belch, vomit, and have no gas bloat syndrome, and it is reversible. The technique, however, is still under long-term trials.

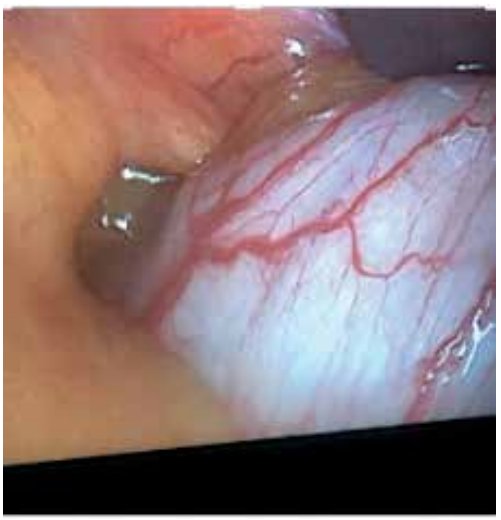

Figure 6.
Laparoscopic view of big hiatus hernia in patient presented with GERD.

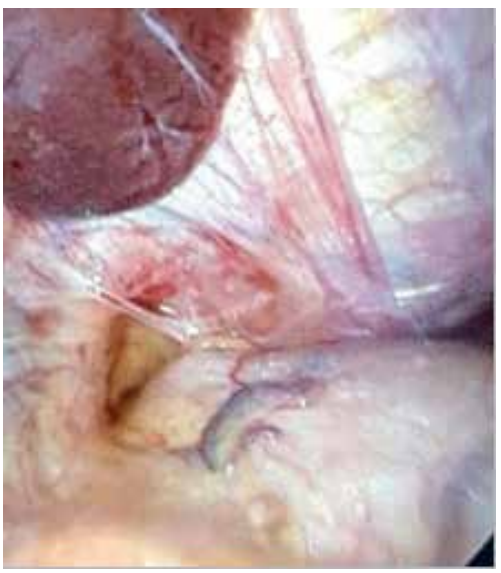

Figure 7.
Laparoscopic view of hiatus hernia in patient came with GERD symptoms.

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Chapter 2

Challenges to Unravel Mechanisms of GERD

Shouji Shimoyama

Abstract

Gastroesophageal reflux disease (GERD) encompasses a spectrum of disorders caused by a reflux of gastric contents into the esophagus or complications of gastroesophageal reflux. Although depending on the definition, the prevalence of GERD is higher in the West than in the East, and the prevalence has been slightly increasing, so that the clinicians, even though they are not gastroenterologists, must encounter GERD patients and treat them. However, the clinicians do feel difficulty in treating GERD patients, since prescription of acid neutralizing agents, such as proton pump inhibitors (PPIs), sometimes fail to resolve their complaints. This may be partly explained by the discrepancies between clinical complaint and endoscopic findings; some patients present endoscopic esophagitis while some do not, and be partly explained by the potentially wide spectrum of pathophysiological etiologies than has been thought. This chapter describes current knowledge on heterogeneous mechanisms of GERD development. Clarifying the mechanisms of GERD on the individual basis may realize conceptual shift from uniform prescription of acid neutralizing agents to establishment of patient-oriented therapies.

Keywords: gastroesophageal reflux disease, nonerosive reflux disease, esophagitis, reflux hypersensitivity, functional heartburn, central sensitization, proton pump inhibitors

1. Introduction

Gastroesophageal reflux disease (GERD) is defined as a condition with at least weekly troublesome symptoms due to the abnormal reflux of stomach contents into the esophagus [1]. Heartburn and/or acid regurgitation are ranked 7th on the list prompting visits to doctors, and GERD is the most common diagnosis given in outpatient visits [2]. GERD appears worldwide with some geographic variation. Prevalence estimates are 18–28% in North and South America, 9–33% in the Middle East, 12% in Australia, but less than 10% in East Asia [3]. In addition, an analysis of temporal trends suggests a particular increase in GERD prevalence in North America and Europe [4], while such a trend in Asia is indeterminable [4–6], partly due to the regional variation of prevalence being much higher in Southwest and Western Asia than in Eastern Asia [6]. In Japan, the prevalence of GERD was below 10% in the 1980s but has shown a two- or three-fold increase in the twenty-first century [7]. Although such time-trends or steady increases in the rise in the number of patients might be attributable to an increased awareness of the disease, and the prevalence of GERD varies between studies, the worldwide disease burden confirms that the numbers of patients suffering from GERD is substantial. Since

the symptoms do compromise patient quality of life (QOL) [8], clinicians, even if they are not gastroenterologists, may frequently encounter such patients and should treat them.

Acid-suppressing agents, such as proton pump inhibitors (PPIs), are a main choice of medication [9]; however, it is also true that while most patients do respond it, some do not. A recent study of PPI use has demonstrated that 20–26% of GERD patients showed persistent heartburn of any intensity for 2 or 3 days or more per week [10]. Recent systematic reviews found that 17–45% of GERD patients experienced persistent troublesome heartburn or regurgitation despite PPI therapy [11, 12]. That not all GERD patients can attain complete relief of GERD symptoms suggests that GERD is likely to be a heterogeneous disease entity which may explain the above unmet clinical needs. In light of the fact that patient QOL deteriorates by PPI refractoriness [13] as well as GERD symptoms *per se*, even if persistent symptoms are mild [14], clarifying the mechanisms of GERD or PPI refractoriness enables clinicians to prescribe medications according to the underlying mechanism on a patient-by-patient basis, which subsequently realizes clinical improvement.

This chapter discusses the current knowledge on the underlying mechanisms of PPI refractory GERD, and considers potential research directions attempting to resolve its symptoms, especially those among PPI refractory patients.

2. Reflux symptoms do not necessarily coincide with endoscopic findings

One of the complex phenomena that impedes the understanding of GERD is that reflux symptoms, endoscopic findings, and treatment results do not necessarily coincide with each other, despite the fact that GERD symptoms are by definition caused by the abnormal reflux of gastric contents into the esophagus. GERD is divided into reflux esophagitis and nonerosive reflux disease (NERD), which is a condition of reflux symptoms with no endoscopically apparent damage to the esophageal mucosa. A substantial proportion (50–70%) of GERD patients demonstrates endoscopically negative findings [15, 16], suggesting that NERD forms the main body of GERD. Curiously, endoscopic healing of erosive esophagitis does not necessarily result in symptom relief. In the same sense, a novel potassium-competitive acid blocker, vonoprazan, achieved improvement of heartburn in only approximately 20% of NERD patients [17]. These results suggest that the association of esophageal acid exposure with patient symptoms is tenuous in a certain fraction of GERD patients. On the other hand, some patients with endoscopically confirmed esophagitis are asymptomatic. Consequently, the prevalence and treatment success rate of GERD are greatly influenced by its definition, i.e., whether or not the study body includes NERD patients, whether or not it includes asymptomatic erosive reflux esophagitis patients, and whether or not treatment success includes only complete symptom relief or extends an even partial response.

3. Mechanisms

3.1 Conventional theory: acid as a direct contributor

Traditionally, reflux esophagitis is thought to be a condition resulting from a caustic, chemical injury inflicted by refluxate components such as hydrogen ions and pepsin. Hydrogen ions injure the superficial layer of the esophageal mucosa and cause esophagitis, and pepsin destroys the tight junction of the esophageal epithelium.

These chemical injuries lead to dilatation of the intracellular spaces (DIS) and an increase in paracellular permeability, which eventually allows acid to penetrate into deep layers of the esophagus, followed by the attraction of inflammatory cells, and finally stimulates nocireceptors [18]. In this theory, the epithelial injury triggers the pathophysiological cascade of GERD, beginning at the luminal surface of the esophageal epithelium, and then proceeds to the deeper layer. This mechanism is readily plausible for GERD patients with esophagitis; however, acid penetration through DIS as a main causative mechanism of GERD cannot explain why PPI refractory patients still exist as do symptomatic patients without esophagitis.

3.2 New theory: GERD is an immune mediated injury

On the other hand, the literature contains some experimental data which cannot necessarily be explained by the conventional theory, namely, acid penetration through DIS as a cause of GERD. In a rat reflux esophagitis model, inflammatory cells appeared at the deep layer of the epithelium, and then infiltrated upward to the superficial layer of the esophagus [19]. Basal cell and papillary hyperplasia preceded the development of esophagitis [19]. Consistent results were demonstrated in a human study, where stopping the PPI therapy in successfully PPI treated patients was associated with T-lymphocyte infiltration in the deep layer of the esophagus as well as basal cell and papillary hyperplasia without apparent surface erosions [20]. Degrees of DIS in patients with reflux esophagitis or NERD did not differ from those of asymptomatic healthy volunteers [21].

Evidence has been accumulated that pro-inflammatory cytokine release from esophageal epithelium, mesenchymal cells, and endothelial cells is an initial event of GERD. The participants of pro-inflammatory cytokines are interleukin (IL)-8 [19, 22, 23], IL-1 beta [19, 23], monocyte chemoattractant protein 1 (MCP-1) [24], IL-6 [25], IL-33 [26], tumor necrosis factor (TNF)-alpha [27], prostaglandin E2 [28, 29], hypoxia inducible factor (HIF)-2alpha [30], and platelet activating factor (PAF) [31, 32]. These pro-inflammatory cytokines attract immune cells—lymphocytes and polymorphonuclear cells—into the esophageal mucosa and submucosa. Interestingly, antineutrophil serum was found to inhibit inflammatory markers in rat acute esophagitis [33].

Another source of pro-inflammatory cytokines is the proteinase-activated receptor 2 (PAR2) localized on the surface of epithelial cells. PAR2 is activated by trypsin and weak acid, then stimulates pro-inflammatory cytokine release such as IL-8 from the epithelial cells, induces a neuroinflammatory effect mediated by neurotransmitters such as substance P and calcitonin gene-related peptide (CGRP), and subsequently establishes visceral hypersensitivity [34]. Indeed, PAR2 expression increases in patients with erosive esophagitis as well as NERD [34]. PAR2 activation has been correlated with IL-8 expression and further with DIS, papillary hyperplasia, and intraepithelial lymphocyte density [34]. These mechanisms mediated by pro-inflammatory cytokines would partly explain why PPI solely cannot necessarily resolve GERD symptoms and why a protease inhibitor, i.e., camostat mesilate, is effective in patients in whom GERD symptoms are caused by weakly acidic episodes.

Weak acid activates acid-sensing nocireceptors such as the transient receptor potential channel vanilloid subfamily receptor-1 (TRPV-1) [35, 36] and acid-sensing ion channels (ASIC) [37]. TRPV-1 is also activated by pro-inflammatory cytokines. TRPV-1 is a detector of various noxious stimuli including heat, acid, and irritant pollutants [38, 39]; it thus has been recognized as an initial molecule of nociceptive transmission. Once activated, neurotransmitters such as substance P and CGRP are released, afferent neurons evoke a sensation of burning pain, and finally peripheral and central sensitization is established. The activation of TRPV-1

also produces PAF [31] and adenosine triphosphate (ATP) [40], the former acting as a chemoattractant of inflammatory cells [41], while the latter stimulates both substance P and CGRP release from esophageal submucosal neurons [40] as well as the secretion of pro-inflammatory cytokines at the esophageal epithelium [35]. ATP *per se* is also a neurotransmitter [42] involved in the sensation of pain. Interestingly, an increased expression of TRPV-1 was observed not only in erosive esophagitis but also in NERD patients without correlation with acid exposure [43].

Taking all these processes into account, while not fully elucidated, it is conceivable that the secretion of pro-inflammatory cytokines, decreased mucosal integrity, exposure of subepithelial nerves to acid, and neuropeptide release to transmit nociceptive stimuli through the peripheral nerve to the brain may interplay to manifest GERD symptoms. Once such a network operates, patients have a lower threshold for pain perception by chemical or mechanical stimulation. The above findings support the hypothesis that an immune mediated neuroinflammatory cascade may underlie the development of GERD symptoms, and that GERD is an immune mediated injury rather than a chemical burn. This hypothesis considers that the secretion of pro-inflammatory cytokines is an initial event, the release of a variety of mediators is the second, and then the transmission of pain through the peripheral nerve to the central nervous system is the last step of the cascade. This cascade contrasts sharply with the conventional theory in which caustic acid-induced direct epithelial injury is an initial event of GERD; it could explain why not all GERD symptoms can be regulated solely by acid suppression. This is an essential background to the clinically reiterating and troublesome claim that there is a distinction between endoscopically-based and symptom-based GERD diagnosis.

4. PPI-refractory GERD comprises heterogeneous pathophysiological conditions

Under the above new theory, the primary focus should be on which factors switch on the cascade. The advent of multichannel intraluminal impedance-pH monitoring enables us to count the number of reflux events, to measure acidity of reflux content, and to differentiate between liquid and air in a refluxate. This technique clarifies that the initial event that triggers the cascade at the esophagus is not only acid exposure but also weak acid or weak alkaline conditions, temperature, electrical stimuli, and mechanical stimuli [44–48]. More detailed analyses of content and pH in the refluxate as well as degrees of symptom-reflux association create challenges to classify PPI-refractory GERD into three subcategories: (1) true GERD, in which symptoms are associated with acid reflux but acid neutralization is incomplete; (2) reflux hypersensitivity, where symptoms are associated with nonacid reflux; and (3) functional heartburn, where symptoms are exerted by nonacid and nonreflux events. The second and third subcategories could be putative factors that are responsible for PPI refractoriness or symptomatic NERD (**Figure 1**). Recently, the Rome IV classification [49] involves these mechanisms as underlying mechanisms of PPI-refractory GERD that allows a paradigm change for understanding this condition.

Reflux hypersensitivity is a heightened perception of physiological reflux which results in persistent GERD symptoms despite PPI therapy [44]. This is characterized by normal acid exposure in the distal esophagus but symptoms are attributable to reflux. On the other hand, functional heartburn is distinct from reflux hypersensitivity, in that functional heartburn is characterized by normal acid exposure in the distal esophagus without any apparent symptom-reflux association. That baseline impedance was reduced in erosive gastritis and acid-associated GERD but not in functional heartburn suggests that functional heartburn is caused by factors other than acid [50].

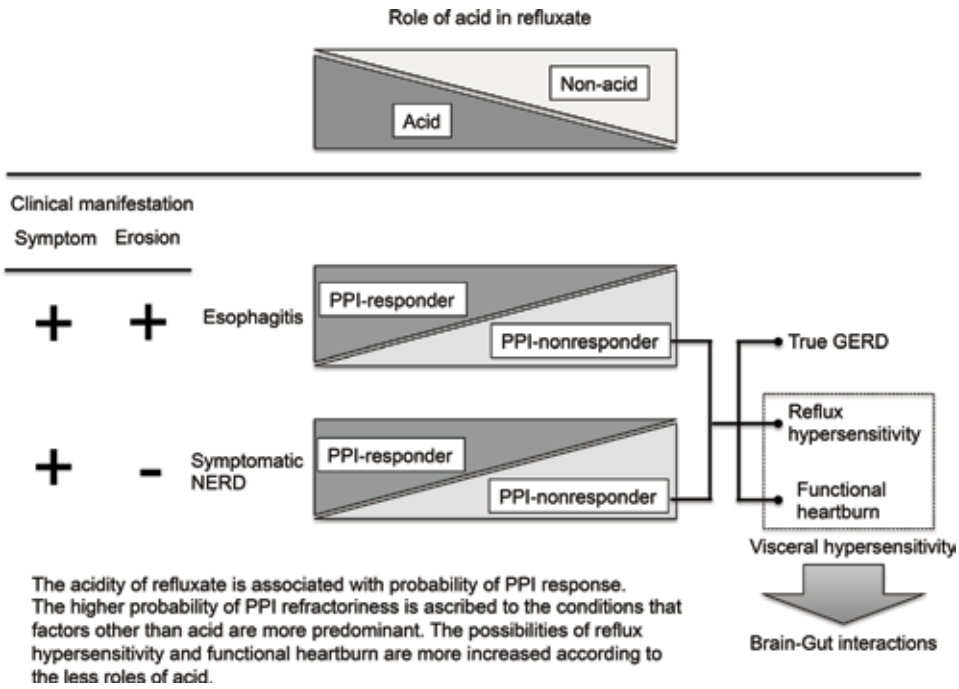

Figure 1.
The acidity of refluxate is associated with probability of PPI response. The higher probability of PPI refractoriness is ascribed to the conditions that factors other than acid are more predominant. The possibilities of reflux hypersensitivity and functional heartburn are more increased according to the less roles of acid.

In this regard, peripheral and central sensitization has recently provided insight into mechanisms establishing of esophageal perception and symptom exacerbation unrelated to acid reflux. Peripheral neuron stimuli triggers repeated neurotransmitter release, and repetitive peripheral firing causes increased excitability of afferent nerves that could establish central sensitization [51]. The upregulated nociceptive pathways could lower resting esophageal pain thresholds, resulting in amplified responses to painful stimuli (hyperalgesia), or resulting in pain perception to non-painful stimuli (allodynia). In this condition, minor physiological noxious stimuli or even innocuous stimuli can be interpreted by the patient as a major symptom, and once hypersensitivity is established, it could continue to potentiate pain even after the stimuli is discontinued, thus "acid" would no longer be a major cause.

In this context, psychiatric comorbidity or psychological stressors could be causes of, or amplifying factors of peripheral and central sensitization. Psychological distress [52], anxiety [53], depression [53], poor sleep quality [54–57], decreased general well-being [58–60], and environmental stress [61] are associated with PPI-refractory GERD. The improvement of reflux symptoms by interventions aimed at reducing stress suggests that the brain-gut interaction and cerebral processing [62] might be responsible for this condition. These psychological factors may compromise esophageal motor function by affecting the enteric nervous system and can modulate esophageal perception, making patients pay excessive attention to intraesophageal events, and consequently cause perception and interpretation of these esophageal events as painful (hypervigilance). By contrast, however, several studies have failed to demonstrate such interaction. Psychological distress was not associated with treatment failure [63]. The relative risk of anxiety or depression in PPI failure was minimal, with the odds ratio being 1.15 [64]. The plausible explanations for these inconsistent results are that the degrees of influence on the enteric nervous system are different between patients

even under the same psychiatric stress. Alternatively, the difference in psychiatric medication given to each patient may play a role. Undoubtedly, the manifestation of GERD symptoms due to a greater psychiatric background should be more likely to be approached by psychotherapy.

This subclassification is clinically important in that true GERD is expected to respond to enhanced or double dose PPI therapy or be a candidate for antireflux surgery, while reflux hypersensitivity and functional heartburn are assumed to show scant response to it. Therefore, it is important to clarify the weight of each component and dominancy in the PPI refractory patients. In a study of 329 NERD patients, 40% showed abnormal acid exposure (true GERD), 36% had reflux hypersensitivity, and 24% had functional heartburn [65]. Another study demonstrated that 40% of 171 symptoms in the PPI refractory GERD patients were considered reflux hypersensitivity, while acid related GERD was only 4.7% [66]. A recent study to explore the composition of 4296 reflux events in 78 PPI refractory patients elucidated that reflux contents are heterogeneous: 24% of reflux events were caused by gas, and 55% of patients were nonacid and reflux unrelated [67]. Finally, as many as 58% of GERD symptoms or 52% of PPI-refractory GERD patients fall into the functional heartburn category [68, 69].

Perhaps background causative factors are mixed, and the extent to which each factor contributes to PPI-refractory GERD is different between patients. Those who are currently categorized as PPI refractory GERD with their manifestations deemed uniform may in fact have heterogeneous etiologies, and therefore a more tailored treatment on the basis of each multifaceted pathway is anticipated to resolve their symptoms better.

5. Therapeutics

By gaining increasing recognition of these mechanisms, therapeutic possibilities could be widened by understanding which individual element is dominant in eliciting GERD symptoms and by diminishing the sensory threshold of what is perceived as painful. Several drugs targeting one of these mechanisms are already in phase III trials, while others are in a developmental stage.

Since the prostaglandin (PG) E2 receptor, EP1, mediates pain perception [70], attempts have been made to reduce PGE2 production or to block EP1 for the treatment of GERD symptoms. There are several randomized, placebo-controlled crossover studies using diclofenac (reduce PGE2 production), ONO8539, and ZD6416 (both EP1 antagonists). Acid induced heartburn was attenuated by diclofenac [71], ONO8539 [72], and ZD6416 [73] as compared with a placebo. As discussed earlier, TRPV-1 activation in primary afferent neurons evokes the sensation of burning pain and induces neurogenic inflammation. Thus the TRPV-1 antagonist, AZD1386, is expected to reduce responses to noxious stimuli; however, the effect has been limited. It was able to increase the pain threshold to heat in healthy men [74] but failed to change the threshold in patients with GERD and partial PPI responders [75].

Several randomized trials focusing on modulating neurotransmitters or the downstream central nervous system have been reported. Pregabalin, a pain modulator including substance P, was able to inhibit the development of acid-induced esophageal hypersensitivity [76]. In order to alleviate the central hypersensitivity, antidepressant nortriptyline was investigated in 20 NERD patients [77]. Functional brain imaging by magnetic resonance revealed that nortriptyline was found to reduce more significantly brain response to esophageal acid perfusion than did placebo. However, this reduction could not improve mental outcome. A

randomized controlled trial to investigate the efficacy of antidepressant imipramine in patients with esophageal hypersensitivity or functional heartburn is underway [NCT01753128].

In an animal study, rikkunshito, a mixture of eight herbal ingredients, was able to reduce neuronal activation and peripheral sensitization through the inhibition of substance P and CGRP expression [78].

6. Future perspectives

The mechanisms that exert GERD symptoms in patients lacking esophageal mucosal injury and/or apparent reflux events remain an area of intense research because these patients often show resistance to PPI therapy, and such refractoriness compromises patient QOL. There is increasing evidence that multifactorial determinants including the number of reflux episodes, the acidity of the refluxate, reflux volume, liquid/gas composition, esophageal hypersensitivity, and cognitive hypervigilance form a fine network to generate GERD symptoms. Although acid is corrosive, the less the roles of acid or mucosal injuries are, the more peripheral and central sensitization become important. The advancement of novel diagnostic tools focusing on impedance, neuropathophysiology, and psychometrics could help identify GERD phenotypes more precisely and practically. These novel metrics could also facilitate an understanding that underlying backgrounds of GERD are diverse, response to treatment is variable, and mechanistic phenotypes are heterogeneous, including hypersensitivity and hypervigilance. Therefore, the traditional single approach of focusing solely on acid suppression makes treatment results unsatisfactory and problematic. Otherwise, an expanded consideration of such multifactorial determinants deserves merit. Each determinant could be a potential therapeutic target, and given the wide array of potential therapeutic targets, the development of drugs to control each target could therefore increase treatment possibilities. Therefore, determining which factors are responsible for GERD symptoms on a patient basis can establish more effective and individualized treatments, leading to the treatment concept that there is no longer a "one size fits all." This conceptual shift will realize the prescription of tailored, more effective drugs as well as the performance of behavioral intervention, and ultimately, fill the current therapeutic gaps.

7. Conclusions

The underlying mechanisms of GERD, especially PPI refractory GERD, are multifactorial. Evidence has been accumulated which supports the concept that GERD is established by a cascade starting from cytokine release to central sensitization. Since each component could be a therapeutic target, it is important to develop novel metrics to quantify the weight of each component and to develop drugs to control each component. Clarifying which component is predominant on the patient-by-patient basis could help realize tailored treatment.

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Chapter 3

Refractory Gastroesophageal Reflux Disease (GERD) Symptoms

Xia Chen and Fei Wang

Abstract

Gastroesophageal reflux disease (GERD) is a chronic condition in which patients suffer troublesome symptoms and/or complications as the reflux of stomach contents occurs. GERD is a common disease worldwide with the range of estimated prevalence 18.1–27.8% in North America, 8.8–25.9% in Europe, 2.5–7.8% in East Asia, 8.7–33.1% in the Middle East, 11.6% in Australia and 23.0% in South America. It causes significant morbidity, considerable decrease of quality of life and high costs of exams and treatment derived from repeated visit doctor. The patients with GERD suffer from typical symptoms such as heartburn and regurgitation, as well as other atypical symptoms including chest pain, cough, asthma, and hoarseness. With the usage of pump inhibitors (PPIs) in clinic, a dramatic improvement in symptom resolution and life quality, as well as in mucosal healing is expected. However, the treatment of GERD fails in a proportion of patients despite the high efficacy of PPIs. This situation is getting more and more common in clinical practices. In this chapter, we will discuss about this difficult situation, emphasizing diagnosis and treatment, combined with suggested management of these patients.

Keywords: gastroesophageal reflux disease (GERD), refractory proton pump inhibitor (PPI) symptoms, high-resolution manometry (HRM), impedance-pH monitoring, refractory reflux symptoms

1. Introduction

Gastroesophageal reflux disease (GERD) is a chronic condition in which patients suffer troublesome symptoms and/or complications as the reflux of stomach contents occurs. GERD is a common disease worldwide with the range of an estimated prevalence of 18.1–27.8% in North America, 8.8–25.9% in Europe, 2.5–7.8% in East Asia, 8.7–33.1% in the Middle East, 11.6% in Australia, and 23.0% in South America [1]. It causes significant morbidity, considerable decrease of quality of life, and high costs of exams and treatment derived from repeated visits to the doctor.

The patients with GERD suffer from typical symptoms, such as heartburn and regurgitation, as well as other atypical symptoms including chest pain, cough, asthma, and hoarseness. With the usage of proton pump inhibitors (PPIs) in the clinic, a dramatic improvement in symptom resolution and life quality, as well as in mucosal healing, is expected.

However, the treatment of GERD fails in a proportion of patients despite the high efficacy of PPIs. This situation is referred as to refractory GERD symptoms. What is worse, it is getting more and more common in clinical practices. In this

chapter, we will discuss about this difficult situation, emphasizing on diagnosis and treatment, combined with suggested management of these patients.

2. Definition of refractory GERD symptom

The definition of "refractory GERD" has traditionally been described as a group of varying symptom presentations related to GERD, which persists even though the patients accepted the standard daily PPI therapy for at least 12 weeks. Some researchers referred to a failure to achieve satisfactory symptomatic response, for example, less than 50% improvement of relief of symptoms and life quality, to once-daily PPI to be classified as "refractory GERD" or "refractory reflux symptoms" [2]. The continued symptoms must be to a degree that impairs quality of life, and symptoms must be "reflux-related," which are supposed to be influenced by sex, age, ethnicity, social status, comorbidity, and cultural background. However, there is a controversy of the PPI dose for the definition of "refractory GERD." Some investigators prefer that inadequate response to twice-daily PPI treatment as refractory disease [3]. Moreover, the patient's remaining symptoms are subjective to and dependent on the patient's expectations of the therapy. It needs more clinical practice and further researches to supplement the definition in the future.

3. Causes of refractory GERD symptom

There are some underlying causes of refractory GERD. Firstly, poor compliance and adherence should be excluded before further evaluation is pursued. There are some key points of medication administration for patients, such as taking PPIs at the optimal 30–60 minutes prior to meal; avoiding discontinued PPIs without doctors' instruction even though the symptoms are relieved; receiving enough information about PPIs therapy. These points are initial important considerations for resolving the refractory GERD. Then, other disorders with GERD-like symptoms, such as esophageal disorders and functional gastrointestinal disorders, should be considered in the differential diagnosis of patients with persistent symptoms (**Figure 1**).

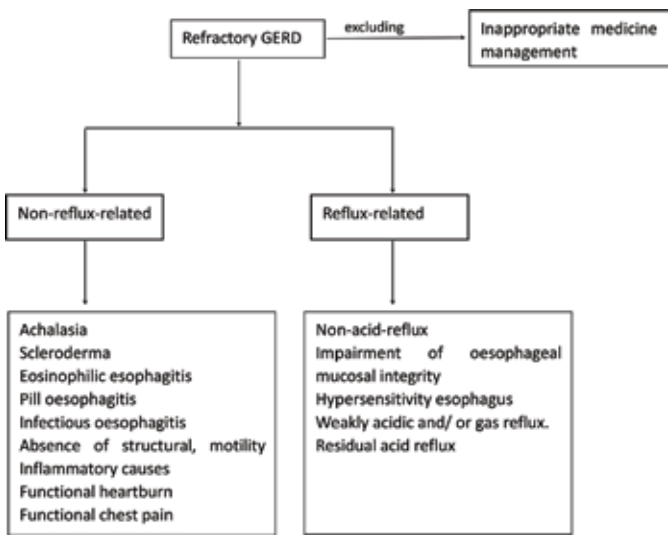

Figure 1.
Causes of refractory GERD symptom.

Additionally, obesity and overeating are other common factors associated with PPI failure in patients initially diagnosed with GERD.

4. Diagnosis of refractory GERD symptom

4.1 Symptom evaluation

The first important step is to identify the actual nature of the persisting symptoms. It can help a physician to choose the correct equipment for the next step of diagnosis. The typical symptoms of GERD are heartburn and regurgitation, which can be recognized by the GerdQ questionnaire. It is a revision of the Reflux Disease Questionnaire (RDQ) with positive predictor questions about heartburn and regurgitation as well as negative predictors about epigastric pain and nausea. It is reported that there is a sensitivity of 65% and specificity of 71% with GerdQ, which is close to the efficiency done by the clinical judgment of gastroenterologists [4]. However, presenting regurgitation should also be differentiated to gastroparesis or rumination syndrome. Except that, the physician should be aware of the proportion of patients with the atypical symptoms, such as retrosternal discomfort and pain, cough, asthma, hoarseness, throat discomfort, foreign body sensation in throat, globus sensation, belching, dysphagia, and epigastric pain and epigastric discomfort.

A recent study shows that there is about half of patients with atypical symptom, combined or uncombined with typical symptom [5]. In short, it is essential to figure out which symptoms respond and which do not respond to PPI therapy. More detailed questioning about symptom often help clarify the cause for a patient's persistent symptoms. Especially, the patients with atypical symptom might have poor response to PPI therapy because there are probably other causes or diseases that overlapped GERD.

4.2 Endoscopy

Upper endoscopy should be taken principally to exclude non-reflux esophageal disorders and other gastric diseases and to check whether erosive esophagitis exists, which can provide evidence of ongoing acid reflux. However, endoscopy is of limited value for diagnosis of refractory GERD symptom. It is because that most patients have normal endoscopy. The potential reasons are that most patients with refractory GERD symptom have other esophageal motility problem; they have non-erosive reflux disease (NERD); or PPIs they taken has healed the mucosal injury.

4.3 Esophageal manometry

All patients with refractory GERD symptom are strongly recommended to undergo esophageal manometry. The purpose mainly is to find esophageal motor disorders, for example, achalasia, weak peristalsis, hypertensive esophageal dysmotility, diffuse esophageal spasm (DES), hiatus hernias (HH), high UES pressure, and abnormal lower esophageal sphincter (LES) pressure. Secondly, but more important, esophageal manometry is applied for identifying the accurate location of LES in order to place reflux monitoring pH sensors.

4.4 Ambulatory monitoring for reflux

There are two methods for esophageal reflux monitoring, called as On-PPI and Off-PPI. In off-PPI (7 days after cessation of PPI), the presence of abnormal acid reflux and/or positive symptom-reflux relationship can be confirmed. The relevant

Nonerosive reflux disease (NERD)	No mucosal break Normal esophageal acid exposure
Hypersensitive esophagus (HE)	No mucosal break Normal esophageal acid exposure SI > 50%, SAP > 95%
Functional heartburn (FH)	Heartburn refractory to PPIs, no mucosal break, normal esophageal acid exposure SI < 50%, SAP < 95%

Table 1.
Diagnosis based on endoscopy, esophageal manometry, and ambulatory monitoring for reflux.

parameter to be observed is esophageal acid exposure, which is the proportion of time (in minutes or percentage of time) spent below pH 4, as well as correlation between symptoms and reflux events (symptom index (SI) and/or symptom association probability (SAP)). Positive symptom association with normal esophageal acid exposure is considered hypersensitive esophagus (HE), reflecting an underlying visceral hypersensitivity. For on-PPI reflux monitoring, impedance-pH monitoring should reasonably be proposed as the preferred investigation. It can detect nonacid reflux during the PPI therapy period, which is one of causes for persistent GERD symptom. It also can figure out whether acid reflux is controlled or not by the treatment (**Table 1**).

4.5 Assessment and evaluation for psychological status

Psychological disorders such as hysteria, anxiety, and distress should also be evaluated in patients with refractory symptoms. Weak correlation of symptoms with acid reflux events might indicate a high level of anxiety and hysteria as compared with patients who demonstrate a close correlation between symptoms and acid reflux event [6]. Anxiety and depression have been shown to increase reflux symptoms reported in population-based studies. A study has reported that patients who did not respond to PPI treatment were suffered from more psychosocial problem [7].

5. Management of refractory GERD symptom

5.1 Lifestyle modifications

Weight loss, head of bed elevation, and avoiding late-night meals, which have been shown as effective interventions for GERD, have not been demonstrated yet equally useful in patients with refractory reflux symptoms. The value of lifestyle modifications in patients with refractory symptoms lies in avoidance of specific lifestyle activities that have been identified by patients or physicians to trigger symptoms. A low-bulk and low-fat diet along with small but more frequent meals should surely be recommended.

5.2 Medicine

Increasing the PPI dose or to change to an alternative PPI improved the symptom in some patients [8]. However, this dosing strategy should be used for a short time period (2–3 months) and should be tapered if it does not result in improvement of symptoms. The addition of an H2RA at bedtime was shown to significantly reduce the duration of nocturnal acid breakthrough (NAB) pain modulators. Transient lower esophageal sphincter relaxation (TLESR) reducers can be considered for patients with abnormal frequency of nonacid reflux. The drugs that can reduce the number of reflux events regardless of their acidity are theoretically desirable

because of the potential for weakly acidic or bile reflux to cause symptoms. Nevertheless, high-quality controlled trials are needed to demonstrate its efficacy in patients with refractory symptoms.

Visceral pain modulator therapy has been another option for patients with an acid-hypersensitive esophagus or functional heartburn. A randomized, placebo-controlled trial has demonstrated citalopram 20 mg/day to be of symptomatic benefit in patients with acid-hypersensitive esophagus and refractory GERD symptoms [9].

5.3 Endoscopic therapy

Stretta procedure and EsophyX transoral incisionless fundoplication are two antireflux endoscopic devices which are clinically available. The Stretta procedure showed clinical improvement of esophageal symptoms and a decrease in PPI use but no significant effect on esophageal acid exposure [10]. EsophyX offers a less invasive alternative to laparoscopic fundoplication for PPI-dependent GERD patients, which still needs further studies to demonstrate its efficiency.

5.4 Antireflux surgery

Comparing with patients with adequate PPI symptom control, antireflux surgery might have a less favorable clinical outcome for the patients with refractory GERD symptom. Normal acid exposure and the presence of atypical reflux symptoms and persisting symptoms despite PPI therapy are predictors of a poor postoperative outcome. It is important to confirm pathological reflux before considering antireflux surgery if there is no proven esophagitis. Summarily, surgery can be a valuable option in patients with typical reflux symptoms with inadequate response to PPIs, provided abnormal esophageal acid exposure and/or positive symptom association analysis in off-PPI test [11].

5.5 Psychological treatment

According to a recent research, perceptions of reflux symptoms are associated with psychosocial distress in these patients with refractory GERD symptom who

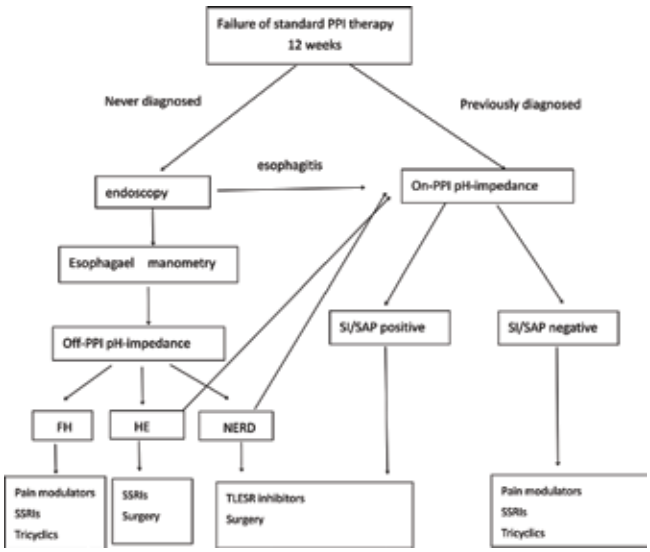

Figure 2.
Diagnostic and treatment algorithm for patients with refractory GERD symptom.

have normal impedance-pH results. Furthermore, patient-reported symptom severity is associated with physiological differences, as opposed to psychosocial factors [11]. In these patients with psychological disorders, treatment-targeted psychosocial abnormality may improve patient response to PPI therapy [2]. Psychological treatment should be a potential consideration in the case of the patients without other identifiable causes. In many clinical experiences, psychological disorders may be an underlying etiology in many patients with refractory symptoms (**Figure 2**).

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Chapter 4

Clinical Picture of Gastroesophageal Reflux Disease in Children

Paolo Quitadamo and Annamaria Staiano

Abstract

Gastroesophageal reflux (GER), defined as the passage of gastric contents into the esophagus, is a normal physiologic process occurring several times per day in healthy infants, children, and adults. The majority of GER episodes occur in the postprandial period, last in <3 min, and cause few or no symptoms. Conversely, when the reflux of gastric contents into the esophagus causes troublesome symptoms and/or complications, we talk about "gastroesophageal reflux disease (GERD)." Distinguishing physiologic GER from GERD may often be tricky for clinicians, especially in infants. The typical presentation of GERD includes the following symptoms: recurrent regurgitation, vomiting, weight loss or poor weight gain, excessive crying and irritability in infants, heartburn or chest pain, ruminative behavior, hematemesis, and dysphagia. Besides these esophageal symptoms, there is a set of extra-esophageal symptoms, mainly respiratory, which may occur along with typical symptoms or may represent the only clinical picture of GERD: odynophagia, wheezing, stridor, cough, hoarseness, dental erosions, and apnea/apparent life-threatening events (ALTEs). While infantile GER tends to resolve spontaneously and does not deserve pharmacological treatment, GERD management includes lifestyle changes, pharmacologic therapy, and surgery. Therefore, a proper diagnosis of these two conditions, besides other possible conditions mimicking reflux, is crucial in order to target the treatment, avoiding the overuse of antacid drugs that currently represents a major source of concern.

Keywords: gastroesophageal reflux, gastroesophageal reflux disease, vomiting, regurgitation, heartburn, irritability, chest pain, respiratory symptoms, typical GERD presentation, atypical GERD presentation

1. Introduction

Gastroesophageal reflux (GER) is a normal physiologic process occurring several times per day in healthy infants, children, and adults. Most episodes of GER in healthy individuals occur in the postprandial period, last in <3 min, and cause few or no symptoms [1]. In contrast, according to the clinical practice guidelines for the diagnosis and management of reflux in the pediatric population, published by the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN), gastroesophageal reflux disease (GERD) is present when the reflux of gastric contents into the esophagus causes troublesome symptoms and/or complications [2]. Reflux symptoms may vary widely according to age. Therefore, distinguishing physiologic GER from GERD may often be tricky, especially in infants. A proper diagnosis of these two conditions, besides other

possible conditions mimicking reflux, is crucial in order to target the treatment, avoiding the overuse of antacid drugs which currently represents a major source of concern. The clinical picture alone is frequently nonspecific and does not allow, except in older children and adolescents, to detect the actual need for acid suppressive medications. Therefore, instrumental diagnostic testing, such as esophageal combined multiple intraluminal impedance and pH monitoring and upper gastrointestinal endoscopy, are often requested [3].

The typical presentation of GERD includes the following symptoms: recurrent regurgitation, vomiting, weight loss or poor weight gain, excessive crying and irritability in infants, heartburn or chest pain, ruminative behavior, hematemesis, and dysphagia. Besides these esophageal symptoms, there is a set of extra-esophageal symptoms, mainly respiratory, which may occur along with typical symptoms or may represent the only clinical picture of GERD: odynophagia, wheezing, stridor, cough, hoarseness, dental erosions, and apnea/apparent life-threatening events (ALTEs). Moreover, GERD may underlie other signs or conditions, such as impaired quality of life, food refusal, persisting hiccups, abnormal posturing/Sandifer's syndrome, anemia, and bradycardia. Finally, esophagitis, Barrett's esophagus, and esophageal adenocarcinoma are possible acknowledged and worrisome long-term outcomes, especially when GERD is undiagnosed or untreated [3].

As already reported, all the above-mentioned signs and symptoms are variously prevalent and relevant in the different pediatric age groups. Therefore, GERD clinical pictures of infants, children, and adolescents will be treated in separate paragraphs.

2. Clinical picture of physiologic GER and GERD in infants

Regurgitation and vomiting are very frequent in healthy infants, mostly during the first months of life. About 70% of healthy infants physiologically regurgitate several times per day, and in about 95% of them, symptoms disappear without intervention by 12–14 months of age [4, 5]. The term "happy spitter" has been used to identify these patients, in order to highlight the benignity of such condition. Infants regurgitate more frequently than adults due to the large liquid volume intake, the prolonged horizontal position of infants, and the limited capacity of both the stomach and esophagus [6]. Irritability and excessive crying are also very frequent in infants and may present along with regurgitation and vomiting. Therefore, neither regurgitation and vomiting nor irritability and excessive crying, regardless of their severity extent and their extent, are sufficient to diagnose GERD. GERD should be suspected in infants with these symptoms, but none of the symptoms are specific to GERD alone. The major role of history and physical examination in the evaluation of purported GERD is to rule out other more worrisome disorders that present with similar symptoms (especially vomiting) and to identify possible complications of GERD. The vast majority of spitting and crying infants suffer from physiologic GER (also called infant regurgitation), a benign condition with an excellent prognosis, needing no intervention except for parental education and anticipatory guidance, and possible changes on feeding composition. Overfeeding exacerbates recurrent regurgitation [6]. Thickened or anti-regurgitation formulas decrease overt regurgitation [7].

Although reflux does occur physiologically in most infants, clinicians should be aware that there is a continuum between physiologic GER and GERD leading to significant symptoms, signs, and complications. Therefore, a small proportion of symptomatic infants may deserve an instrumental diagnostic assessment for GERD or other GERD-mimicking diseases. To help identify this subgroup of infants, the latest international GER guidelines drafted a list of warning signals requiring investigations in infants with regurgitation or vomiting (**Table 1**).

Gastrointestinal bleeding
Hematemesis
Hematochezia
Bilious vomiting
Consistently forceful vomiting
Onset of vomiting after 6 months of life
Failure to thrive
Diarrhea
Constipation
Fever
Lethargy
Hepatosplenomegaly
Bulging fontanelle
Seizures
Macro/microcephaly
Abdominal tenderness or distension
Documented or suspected genetic/metabolic syndrome

Table 1.
Warning signals requiring investigation in infants with regurgitation or vomiting.

3. Clinical picture of GERD in young children

Whether persisting from infancy or of new onset, regurgitation and vomiting are less common in children older than 18 months of age and deserve an instrumental evaluation to diagnose possible GERD or to rule out alternative diagnosis [2]. Besides regurgitation and vomiting, GERD may present in children with many

Gastrointestinal obstruction
Pyloric stenosis
Malrotation with intermittent volvulus
Intestinal duplication
Hirschsprung disease
Antral/duodenal web
Foreign body
Incarcerated hernia
Other gastrointestinal disorders
Achalasia
Gastroparesis
Gastroenteritis
Peptic ulcer
Eosinophilic esophagitis/gastroenteritis
Food allergy
Inflammatory bowel disease
Pancreatitis
Appendicitis

Infectious
Sepsis
Meningitis
Urinary tract infection
Pneumonia
Otitis media
Hepatitis
Metabolic/endocrine
Galactosemia
Hereditary fructose intolerance
Urea cycle defects
Amino and organic acidemias
Congenital adrenal hyperplasia
Renal
Obstructive uropathy
Renal insufficiency
Toxic
Lead
Iron
Vitamins A and D
Medications—ipecac, digoxin, theophylline, etc.
Cardiac
Congestive heart failure
Vascular ring
Others
Pediatric falsification disorder (Munchausen syndrome by proxy)
Child neglect or abuse
Self-induced vomiting
Cyclic vomiting syndrome
Autonomic dysfunction

Table 2.
Differential diagnosis of vomiting in infants and children.

other signs or symptoms, the most frequent of which are heartburn, food refusal, dysphagia, feeding or sleeping disturbances, failure to thrive, persisting hiccups, impaired quality of life, and dental erosions. Respiratory symptoms, such as chronic cough, wheezing, hoarseness, laryngitis, chronic asthma, aspiration pneumonia, ear problems, and sinusitis, are atypical symptoms possibly associated with GERD. Nevertheless, the paucity of clinical studies, varying disease definitions, and small sample sizes do not allow to draw firm conclusions about their association with reflux [8].

According to the latest international pediatric guidelines, subjective reflux symptom description is unreliable in children younger than 8 to 12 years of age, and many of the purported symptoms of GERD in children are nonspecific [9–11].

Therefore, a clinical diagnosis based on a history of heartburn cannot be inferred since these individuals cannot reliably communicate the quality and quantity of their symptoms [12–16]. GERD testing mainly include esophageal pH/MII, upper GI endoscopy, and barium upper GI series. The diagnosis of GERD has to be inferred when tests show excessive frequency or duration of reflux episodes, esophagitis, or a clear association of symptoms and signs with reflux episodes in the absence of alternative diagnose (**Table 2**).

4. Clinical picture of GERD in older children and adolescents

In older children and adolescents' heartburn, regurgitation and chest pain are the specific symptoms of GERD. According to experts' opinions, in this age group, the description and localization of these symptoms are a reliable indicator for GERD, and an acid suppressive trial may be empirically started, regardless of an objective evaluation of reflux. This approach is mainly driven from adult studies [17, 18]. Along with heartburn and chest pain, other symptoms and signs may occur in older children and adolescents, such as regurgitation, epigastric pain, food refusal, dysphagia, impaired quality of life, sleeping disturbances, anorexia, and dental erosions. Moreover, likewise infants and younger children, even older children and adolescents, may experience respiratory symptoms as the only manifestation of GERD [3].

Several studies report a significant degree of overlap between GERD and functional dyspepsia (FD) [19, 20]. According to the Rome diagnostic criteria for pediatric functional gastrointestinal disorders, FD is defined as a "persistent or recurrent pain or discomfort in the upper abdomen, most often aggravated by meal ingestion, not relieved by defecation or associated with the onset of a change in stool frequency or stool form (i.e., not irritable bowel syndrome) when no physical or organic cause for the symptom is identified with conventional testing" [21].

Clinicians should careful approach upper GI symptoms, being aware that the current literature on the overlap between GERD and FD is affected by considerable heterogeneity in terms of the criteria and diagnostic procedures used to assess both conditions. To exclude GERD, patients must undergo upper digestive endoscopy, pH monitoring, and/or an empiric acid-suppressive trial. A lack of correspondence between symptoms and reflux episodes, together with normal acid exposure in the distal esophagus, would suggest a diagnosis of FD. Finally, clinicians should also be aware that other causes of heartburn-like chest pain including respiratory, cardiac, musculoskeletal, medication-induced, or infectious etiologies should be considered besides GERD.

5. Overview on GERD and respiratory symptoms

As abovementioned, GERD may also underlie respiratory symptoms, such as chronic cough, wheezing, stridor, odynophagia, and hoarseness. Although the role of GERD in the pathogenesis of respiratory symptoms in adults is widely accepted [22], in children there is less evidence to support this relationship [23, 24]. Several pathogenetic mechanisms have been proposed to explain the link between GERD and respiratory symptoms, including aspiration of acid gastric contents into the upper airways, vagal reflex induced by the presence of acid in the esophageal lumen, and sensitization of the central cough reflex [2, 25].

Recent advances in the pathogenesis of reflux-induced respiratory symptoms have followed the introduction in clinical practice of MII-pH, which is available for pediatric use since 2002 [26]. Combined esophageal pH and impedance monitoring offer several advantages over a standard pH assessment, including the ability

of detecting non-acid reflux events, determining the height and composition of the refluxate (liquid, gas, or mixed), recognizing swallows from authentic reflux episodes, assessing the bolus clearance time, and measuring symptom association with reflux (symptom association probability, SAP) even while the patient is assuming acid-suppressive medications [27]. Thanks to pH-impedance studies, several authors have recently highlighted the role of weakly acid and non-acid reflux [28–35]. Furthermore, a recent review reported that a significant percentage of patients with GERD-related respiratory symptoms do not improve despite an aggressive acid-suppressive therapy [36], thus supporting the hypothesis that respiratory symptoms are less related to acidity than GI symptoms.

In conclusion, the analysis of the medical literature concerning the relationship between GERD and respiratory symptoms highlights a large body of evidence often discordant or conflicting, rarely allowing to draw firm conclusions to be used in clinical practice. Over the next years, the use of pH-impedance, combined with manometry or with cardiorespiratory monitoring, in longitudinal, placebo-controlled, double-blind clinical trials, will help in clarifying the main pathophysiological aspects that link GER and respiratory system, providing the clinician with fundamental scientific basis for diagnostic and therapeutic choices.

6. Management of physiologic GER

In newborns and infants, TLESRs are physiological events. Further considering the physiologic poorer tone of the lower esophageal sphincter, the frequency of GER events is commonly much higher compared to the other ages of life. Thus, uncomplicated GER in otherwise healthy infants is classified as physiologic or functional GER. This condition tends to resolve spontaneously in 95% of infants within 12–14 months of life [37, 38]. According to the current international guidelines, infants with functional GER should not receive pharmacological treatment, despite symptoms may cause significant distress to both infants and parents [2]. The most common symptoms associated with GER in the first year of life are regurgitation, vomiting, irritability, cough, and food refusal [39–42]. When physiologic GER is clinically suspected in healthy, thriving infants, parental education, reassurance, and anticipatory guidance are always required and usually sufficient [2].

6.1 Feeding changes in infants

Cow's milk allergy: Infants with cow's milk protein allergy may present with vomiting and regurgitation as well as infants with GER. In order to avoid possible misdiagnoses, formula-fed infants with regurgitation and vomiting could benefit of a 4-week trial with hydrolyzed milk or amino acid formula [43, 44]. Breast-fed infants as well may be affected by cow's milk protein allergy since a few proteins pass into the human breast milk. Therefore, an exclusion of cow's milk proteins from maternal diet should be considered [45–47].

Overfeeding: Although exact numbers are unknown, overfeeding has recently been thought to be a prominent cause of GER because the ingested volume is relatively large compared to the size of the stomach in infants. Large-volume feeds can promote regurgitation in infants due to gastric distention and increase in TLESR frequency [48]. Restricting volume, however, can result in insufficient energy intake. Thus, increasing the caloric concentration of the feedings while decreasing the total volume of the feedings may decrease GER [2].

Thickening feeds: Several studies have demonstrated the efficacy of thickened formula in reduction of reflux events in infants with GER. A thickened formula

was recently tested in premature neonates with apnea. The primary outcome was assessed through multichannel intraluminal impedance, reporting a significant decrease of only acid reflux episodes, while apneic episodes and non-acid GER indexes were not significantly altered [49–51]. The efficacy of thickened formula was demonstrated both on typical and atypical reflux symptoms [52–55]. Despite thickened feeds are currently increasingly being used to treat infants with GER [56], it has been debated that thickened formula increases the caloric intake, thus predisposing infants to later obesity [51, 53, 56–58]. Conversely, infants fed with formula thickened with carob bean gum were reported having a comparable weight increase to the control group [54]. Similar results were with a soy fiber-thickened formula [58]. Furthermore, the fermentation of thickening agents has been reported to cause side effects such as abdominal pain and diarrhea [42]. Further, well-designed clinical trial on these possible side effects are needed in order to evaluate their true relevance.

6.2 Positioning therapy for infants

Positioning of the body may have an impact on the incidence of GER episodes. Therefore, among the conservative measures to manage infantile GER, the current NASPGHAN-ESPGHAN guidelines include positioning strategies. Different positionings have been so far evaluated: semisupine, prone, supine and flat, supine with head elevated, and left-side down and right-side down position [59–66]. Infants with GER were shown having a longer exposure to gastroesophageal reflux in semisupine position, with an infant seat, than in prone position. Therefore, semisupine position is strongly discouraged, especially for infants younger than 6 months of age. The prone position reduces the reflux episodes significantly more than the other positions. However, the increased risk of a sudden infant death syndrome (SIDS) shifts the prone position in a negative cost/benefit ratio. Currently, the prone position is advisable only in infants with demonstrated airway disorders, in which the risk of death from GERD is higher than that from SIDS. Conversely, the prone position may be suggested for all infants in the early postprandial period when they are still awake or in children older than 1 year of age [2].

6.3 PPI abuse in infants

The number of PPI prescriptions for infants has increased manifold over the last years, despite the absence of evidence for acid-related disorders in the majority [66, 67]. This dramatic increase in PPIs' prescribing patterns has raised concerns related to their appropriate use and associated costs [68]. Although irritable infants are frequently empirically treated with PPIs as the reflux esophagitis is believed to be the cause of crying, there is no evidence supporting the usefulness of PPIs, neither as a diagnostic test nor as a treatment strategy in this age group. Double-blind randomized placebo-controlled trials of PPI efficacy in infants with GER symptoms showed that PPIs and placebo produced similar improvement in crying, despite the finding that acid suppression occurred only in the PPI group [6, 69]. In the largest double-blind randomized placebo-controlled trial of PPIs in infants with symptoms purported to be GERD-related, response rates in those treated with lansoprazole or placebo for 4 weeks were identical (54%) [70]. Therefore, no placebo-controlled treatment trial, in which enrollment was based on "typical" GERD symptoms, has demonstrated symptom improvement in infants. Thus, in accordance to the ESPGHAN-NASPGHAN international guidelines, we believe that a serious effort to curtail PPI empiric use in infant is firmly required.

7. Treatment options for GERD

GERD management in children includes lifestyle changes, pharmacologic therapy, and surgery. Lifestyle changes which may contribute to prevent and improve reflux symptoms in infants have already been discussed in the previous sections. In children and adolescents, lifestyle changes include modification of diet and sleeping position, weight reduction, and smoking cessation [2, 71]. Although usually sufficient to manage physiologic GER, lifestyle changes alone are not effective in the treatment of GERD, which must include pharmacologic therapies and possible surgical intervention for severe, unresponsive cases.

The major pharmacologic agents currently used for treating GERD in children are gastric acid-buffering agents, mucosal surface barriers, and gastric antisecretory agents. Since the withdrawal of cisapride from commercial availability in most countries, prokinetic agents have been less frequently used, although domperidone is commercially available in Canada and Europe. Pediatric studies comparing pharmacologic agents for GERD have been impaired by small sample size, absence of controls, and use of unreliable endpoints. Therefore, most studies investigating effectiveness and safety of GERD drugs have been performed in adults, and their applicability to children of all ages is uncertain.

7.1 Histamine-2 receptor antagonists

Histamine-2 receptor antagonists (H^2RAs) inhibit histamine-2 receptors on gastric parietal cells, thus decreasing acid secretion. H^2RAs currently available in most countries are cimetidine, ranitidine, famotidine, and nizatidine. These four drugs have similar spectra of activity, side effects, and clinical indications and are extremely well tolerated by patients [72–79]. However, the efficacy of H^2RAs in achieving mucosal healing is much greater in mild than in severe esophagitis [80]. Extrapolation of the results of a large number of adult studies to older children and adolescents suggests that H^2RAs may be used in these patients for the treatment of GERD symptoms and for healing esophagitis, although H^2RAs are less effective than PPIs for both symptom relief and healing of esophagitis [77, 81, 82]. The fairly rapid tachyphylaxis that develops with H^2RAs is a major drawback to their chronic use. The occurrence of tachyphylaxis, or a decrease of the response, to intravenous ranitidine and the escape from its acid-suppressive effect have been observed after 6 weeks [83], and tolerance to oral H^2RAs in adults is well recognized [84, 85]. In some infants, H^2RA therapy causes irritability, head banging, headache, somnolence, and other side effects that, if interpreted as persistent symptoms of GERD, could result in an inappropriate increase in dosage [79]. H^2RAs, particularly cimetidine, are associated with an increased risk of liver disease [86, 87] and cimetidine with gynecomastia [88].

7.2 Proton pump inhibitors

PPIs act by blocking Na+–K+-ATPase, the final common pathway of parietal cell acid secretion, often called the proton pump, thus inhibiting acid secretion. Studies in adults have shown that PPIs produce higher and faster healing rates for erosive esophagitis than H^2Ras, largely because of their ability to maintain intragastric pH at or above 4 for longer periods and to inhibit meal-induced acid secretion [89]. Moreover, the strong suppression of acid secretion by PPIs also results in decrease of 24-h intragastric volumes, thereby facilitating gastric emptying and decreasing volume reflux [90]. To date, PPIs approved for use in children in North America are omeprazole, lansoprazole, esomeprazole, pantoprazole, and rabeprazole. No

PPI has been approved for use in infants younger than 1 year of age. Most studies of PPIs in children are open-label and uncontrolled [91, 92]. In children, as in adults, PPIs are highly efficacious for the treatment of GERD symptoms and the healing of erosive disease. PPIs have greater efficacy than H^2RAs. Young children may require higher per kilogram doses to obtain the same acid-blocking effect [93–96].

7.3 Prokinetic agents

Although the role of delayed gastric emptying in the pathogenesis of GERD has never been clarified and remains controversial, prokinetic agents have been used as first-choice treatment for reflux symptoms in children for many years. The most well-known prokinetic drug is cisapride, widely prescribed until 2000, when it was withdrawn due to cardiac toxicity which increased the risk of sudden death [97]. Currently, other prokinetics such as domperidone and metoclopramide are still commonly prescribed. Nevertheless, neither have robust evidence to support their use in children with GERD [98–100]. Baclofen is a gamma-amino-butyric-acid (GABA) receptor agonist which has been shown to reduce both acid and non-acid refluxes in adults, probably by inhibiting the transient relaxations of the lower esophageal sphincters (TLESRs) [101]. In children, baclofen was shown to accelerate gastric emptying for 2 h after administration, decreasing the frequency of emesis [102, 103]. Despite its promising effects, many side effects, such as dyspeptic symptoms, drowsiness, dizziness, and seizures, preclude its routine use [104]. In conclusion, there is insufficient evidence to justify the routine use of cisapride, metoclopramide, domperidone, or baclofen for GERD.

7.4 Alginates and antacids

Alginates and antacids are commonly combined in the same product and are widely used by adult patients to treat reflux symptoms. Antacids act by directly buffering gastric contents, thereby reducing heartburn. There is little evidence for the use of antacids in pediatric age [105, 106]. Conversely, alginates have been studied to a greater extent in children. Alginates precipitate in the stomach to form a low-density but viscous gel that forms a foam that floats on the surface of gastric content and can preferentially enter the esophagus instead of gastric content during reflux episodes [107]. Studies performed both in infants and children showed a significant reduction in the height of reflux episodes, along with an improvement of symptomatic scores [108–113]. On-demand use of antacids and alginates may provide prompt relief from reflux symptoms in children and adolescents [114]. Nevertheless, although alginates seem to have a good safety profile, antacids have possible adverse effects, such as increased serum levels of aluminum, magnesium, or calcium, which represent a major drawback to their long-term use [113, 115, 116].

7.5 Surgical therapy

Surgical treatment represents the last option for GERD management. When and which children could likely benefit from anti-reflux surgery (ARS) has never yet been elucidated. Currently, surgery should be considered for children with confirmed GERD who have failed optimal medical therapy, who are dependent on medical therapy over a long period of time, who are significantly nonadherent with medical therapy, or who have life-threatening complications [2]. Medical literature on surgical therapy in children with GERD mainly consists of retrospective case series in which details on GERD diagnosis and on previous medical therapy are partially lacking, making it difficult to evaluate the indications for and the outcomes of

surgery [117–119]. Moreover, most surgical series include children with underlying conditions predisposing to the most severe GERD, such as neurological impairment, thereby confounding efforts to determine the benefits versus risks of surgical anti-reflux procedures in specific patient populations. Nevertheless, according to the available data, ARS in children shows a good overall success rate (median 86%) in terms of complete relief of symptoms, and its outcome does not seem to be significantly influenced by different surgical techniques [120]. Gastric fundoplication is the most commonly performed intervention. Different types of fundoplication have been developed, according to Nissen (360° fundic wrap around the esophagus) and Thal and Toupet (both partial wraps). Traditionally, these procedures were performed open, whereas in most centers, laparoscopic fundoplications are now preferred. Nevertheless, a recent pediatric trial showed that open and laparoscopic fundoplications provide similar control of reflux and quality of life at follow-up, although the latter is associated with reduced incidence of retching persisting over a 4-year period [120–122].

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Chapter 5

The Role of Increased Gastric Acid Secretion and Reactive Oxygen Species in the Pathophysiology of Reflux Esophagitis

Mohamed-Amine Jabri and Hichem Sebai

Abstract

Gastroesophageal reflux (GER) disease is a chronic disease characterized by the recurrent ascension of some of the gastric contents in the esophagus. Indeed, gastric acid secreted by parietal cells and the gastric pepsin activity, but not the intestinal alkaline content, are the most important pathogenic factors of GER. Several pathophysiological mechanisms are involved, the most important of which is the imbalance of the redox state of the esophageal tissue. Indeed, several studies have shown that reflux esophagitis is mediated by oxygen-derived free radicals. In this chapter, we describe the pathophysiology and important pathways, especially acid gastric contents and reactive oxygen species involved in pathology of GER.

Keywords: esophagus, parietal cells, pepsin activity, reactive oxygen species

1. Introduction

Gastroesophageal reflux (GER) is defined as the passage through the cardia of the contents of the stomach into the esophagus, without any effort of vomiting [1]. The intermittent ascent of the gastric contents, particularly the acid in the esophagus, is the main determinant of the esophageal mucosa lesions [2, 3]. The alteration of gastric or esophageal motility, the aggressiveness of the refluxing fluid, and the alteration of esophageal mucosal resistance are also important factors in the genesis of esophagitis lesions [4]. Disturbances of the inflammatory and immune response reported during reflux esophagitis are numerous [5]. It is well established that oxidative stress, by excessive production of oxidizing mediators or by a deficiency of certain nutrients essential to the maintenance of a suitable antioxidant defense, contributes to cellular dysfunctions and to the esophagus tissue destruction [5, 6]. This chapter gives a detailed insight about the role of acidic gastric secretions and the involvement of oxidative stress as well as reactive oxygen species (ROS) in the pathophysiology of reflux esophagitis.

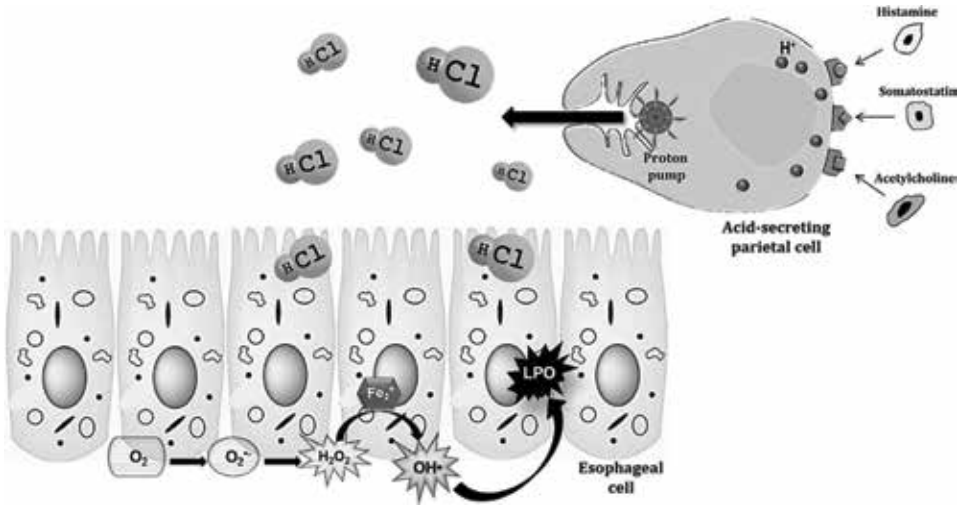

Figure 1.
Mechanism of acidic gastric secretion and production of reactive oxygen species in the esophageal mucosa.

2. Mechanism of acidic gastric secretion

Gastric secretion is essentially characterized by its high concentration of hydrochloric acid. This acidity makes it possible to sterilize the food bowl and initiate digestion, especially food proteins. Gastric acid secretion is permanently modulated by the endocrine (gastrin), paracrine (histamine and somatostatin), as well as nerve (acetylcholine) pathways (**Figure 1**). Gastrin is secreted at the basal pole of the G cells of the pyloric glands of the antrum into the bloodstream. It acts by binding membrane receptors of enterochromaffin-like cells (ELC) by stimulating the secretion of histamine and on the membrane receptors of parietal cells by stimulating the secretion of hydrochloric acid [7, 8].

Histamine is secreted by ELC, in the vicinity of parietal cells, in response to stimulation by gastrin and parasympathetic activation. This secretion is inhibited by somatostatin. Histamine stimulates the HCl secretion by action on the histamine H2-type receptors of parietal cells [9].

Acetylcholine, released by postganglionic neurons from the parasympathetic system, stimulates the parietal cells, gastrin, and histamine secretions. Somatostatin is the main inhibitor of gastric acid secretion: its secretion by D cells is stimulated by increasing the concentration of H^+ ions in the gastric cavity [8].

3. Physiopathology of gastroesophageal reflux

3.1 Failure of the anti-reflux barrier

Generally, GER is related to a failure of the anti-reflux barrier. This anti-reflux barrier is composed of the lower esophageal sphincter (LES), which plays the role of an internal sphincter, and the diaphragmatic muscle that plays the role of an external sphincter. The LES is a zone of high pressure, 2–4 cm long, with no individualized thickening of the circular layer of the muscularis. This area of high pressure separates the thoracic esophagus subjected to negative pressure from the stomach that supports the positive pressure prevailing in the enclosure of the abdominal cavity [1, 10]. The pressure of the LES is influenced by several dietary factors, certain drugs, and circulating hormones. Chocolate, fats, alcohol, and caffeine reduce the pressure of the LES

[4, 10]. Tobacco also lowers the pressure of the LES, and in smokers, the periods of smoking are marked by an increased GER frequency. Many medications affect also the LES pressure. Indeed, anticholinergics, nitrates, theophylline, and anticalcics lower it, while cisapride and metoclopramide increase it [4, 10].

3.2 The reflux material composition

The reflux that reaches the esophagus may be of variable acidity, may be depending on the case of a pure liquid or a mixture of gas and liquid [11]. The role of pepsin in the occurrence of esophageal lesions during GER is uncertain. Animal studies have shown that the toxicity to the esophageal mucosa of an HCl-pepsin mixture is higher than that of a pure acid solution [4, 12]. The reflux of duodenal contents into the stomach is a postprandial physiological phenomenon. It is therefore not unusual for GER to contain duodenal, pancreatic, and bile secretions. In experimental models, conjugated bile acids are toxic to the esophagus at acidic pH, whereas nonconjugated bile acids have a toxicity that is observed mainly at neutral pH. But the human bile acid concentrations in the reflux liquid never reached the concentrations used in these experimental models [11, 12].

Studies in humans have shown that the frequency of duodeno-gastroesophageal reflux is particularly high in patients with severe esophagitis and especially an endobrachy-esophagus, notably in those who respond to treatment with proton pump inhibitors [12].

4. Involvement of oxidative stress in the pathophysiology of reflux esophagitis

Several recent studies have shown that esophagitis induced by gastroesophageal reflux is mediated by reactive oxygen species (ROS) [13–16]. The role of ROS has been extensively studied in gastric and esophageal mucosal lesions induced by the administration of NSAIDs such as aspirin [17] or ethanol [18] as well as by ischemia [6].

4.1 Oxidative stress and production of oxygenated free radicals

Oxidative stress is defined as an excessive intracellular oxidation due to an imbalance between the production of oxidizing species or reactive oxygen species (ROS) and that of antioxidant systems [16, 19]. The equilibrium or redox homeostasis is then disrupted, and the cells become vulnerable to free radical attacks, resulting in oxidative damage to cellular components [20, 21]. Indeed, ROS are responsible for denaturation and degradation of biomolecules and are involved in tissue lesions observed during inflammatory processes [22]. They are produced during various biological processes by a large number of cells, particularly phagocytic cells [23].

4.2 Free oxygen derivatives and caustic injuries of esophagus during GER

According to recent studies on animal models [14, 24, 25], it has been shown that gastroesophageal reflux promotes the production of ROS, which leads to lesions of the esophageal mucosa. Reactive oxygen species appear to be a major cause of esophageal lesion during GER. In point of fact, it has been shown that the administration of a free radical scavenger effectively inhibits esophagitis in rats [6]. The increased production of free radicals derived from oxygen has been accompanied by increased lipid peroxidation of the esophageal mucosa, which is a sensitive marker of membrane damage caused by free radicals [24]. In addition, several previous

studies have shown that GER induced experimentally in rats caused an increase in the level of malondialdehyde, a final product of lipid peroxidation, as well as a decrease in the activity of antioxidant enzymes such as catalase, glutathione peroxidase, and superoxide dismutase in the esophageal mucosa tissues [5, 13, 14]. GER has also induced the decrease of reduced glutathione and thiol group levels as well as plasma scavenging activity, an indicator of free radical generation in tissues [13]. Other studies have shown that blocking acid secretion or administering an antioxidant compound effectively reduced the severity of reflux esophagitis. Indeed, the administration of the various free radical scavengers prevented the esophageal mucosa damage, by stimulating the activity of antioxidant enzymes and inhibiting lipid peroxidation [5, 14].

5. Conclusion

Several mechanisms are involved in the occurrence of GER and in its severity, especially the gastric secretion of acid and pepsin as well as the role of reactive oxygen species. Therefore, the ROS-scavenging compounds should be considered in the prevention and treatment of reflux esophagitis, in accordance with the current antisecretory treatment.

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Gastroesophageal reflux disease (GERD) is a very common, global clinical problem. It affects any age group, both males and females, and is seen mainly in developed countries, especially among obese individuals. GERD needs to be treated to prevent nuisance symptoms and long-term complications. The book deals with the diagnosis of GERD, including clinical presentations and diagnostic investigations, and describes the different available conservative, medical, surgical and endoscopic treatments. The book also covers gastroesophageal disease in children, its presentation and treatment. It also deals with the refractory type of gastroesophageal disease including different theories. It is very useful for gastroenterologists and upper gastrointestinal surgeons.

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