

# Diagnosis and Management of Gastroesophageal Reflux Disease

Guest Editors: Ping-I Hsu, Nayoung Kim, Khean Lee Goh,  
and Deng-Chyang Wu





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## Editorial

# Diagnosis and Management of Gastroesophageal Reflux Disease

Ping-I Hsu,<sup>1</sup> Nayoung Kim,<sup>2</sup> Khean Lee Goh,<sup>3</sup> and Deng-Chyang Wu<sup>4</sup>

<sup>1</sup> Division of Gastroenterology, Department of Internal Medicine, Kaohsiung Veterans General Hospital, National Yang-Ming University, Kaohsiung 813, Taiwan

<sup>2</sup> Division of Gastroenterology, Department of Internal Medicine, Seoul National University Bundang Hospital, Seoul National University, Republic of Korea

<sup>3</sup> Department of Medicine, University of Malaysia, Kuala Lumpur, Malaysia

<sup>4</sup> Division of Gastroenterology, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung 807, Taiwan

Correspondence should be addressed to Ping-I Hsu; [williamhsup@yahoo.com.tw](mailto:williamhsup@yahoo.com.tw)

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Gastroesophageal reflux disease (GERD) is one of the most common disorders in medical practice. It is the most common gastrointestinal diagnosis recorded during visits to outpatient clinics in the United States. Apart from the economic burden of the disease and its impact on quality of life, GERD is the most common predisposing factor for esophageal adenocarcinoma [1].

Recently, many important issues have emerged regarding the classification, pathogenesis, natural history, and treatment of GERD. Although use of proton-pump inhibitor (PPI) is the treatment of choice for GERD, approximately, one-third of patients with GERD fail to respond symptomatically to a standard-dose proton-pump inhibitor (PPI), either partially or completely [2]. Additionally, most GERD patients need long-term treatment for frequent relapses after discontinuing acid inhibition therapy. This has led to great interest in new endoscopic therapies for the treatment of this disease. With regard to the diagnosis of GERD, patients with refractory reflux symptoms and normal upper endoscopy are more difficult to diagnose and treat. Combined 24-hour pH and impedance monitoring allows classifying the patients as having true nonerosive reflux disease (NERD), hypersensitive esophagus, or functional heartburn and is helpful for further management of the patients [3].

The main focus of this special issue is on recent advances in the treatment of erosive esophagitis, NERD and Barrett's esophagus. In addition, the emerging diagnostic methods, pharmacological treatments, and endoscopic therapies for GERD are also discussed.

The paper entitled “*The frequencies of gastroesophageal and extragastroesophageal symptoms in patients with mild erosive esophagitis, severe erosive esophagitis, and Barrett's esophagus, in Taiwan*” is the first work simultaneously assessing the differences in reflux symptom profiles among the three different categories of GERD. The data showed that the frequencies of some esophageal and extraesophageal symptoms in patients with Los Angeles grade A/B erosive esophagitis were higher than those in patients with Los Angeles grade C/D erosive esophagitis and Barrett's esophagus.

In the paper entitled “*Current pharmacological management of gastroesophageal reflux disease*,” Y.-K. Wang et al. present the current and developing therapeutic agents for GERD treatment. The efficacies of PPIs and potassium-competitive acid blocker in GERD therapy are well reviewed. Additionally, the article summarizes the development of novel therapeutic agents focusing on the underlying mechanisms of GERD.

In the paper entitled “*Pharmacological therapy of gastroesophageal reflux in preterm infants*,” L. Corvaglia et al. review the pathogenesis, presentation, diagnosis, and treatment of gastroesophageal reflux in preterm infants. A stepwise approach is advisable for the treatment of gastroesophageal reflux in preterm infants, firstly, promoting nonpharmacological interventions and secondly, limiting drugs to selected infants unresponsive to the conservative measures or who are suffering from severe gastroesophageal reflux with clinical complications.

In the paper entitled “*Stretta radiofrequency treatment for GERD: a safe and effective modality*,” M. Franciosa et al. focus on the safety, efficacy, and durability of the Stretta radiofrequency treatment for GERD therapy. The novel endoscopic treatment reduces esophageal acid exposure, decreases the frequency of transient lower esophageal relaxation, decreases medication use and improves quality of life in GERD patients.

In the paper entitled “*Duodenal tube feeding: an alternative approach for effectively promoting weight gain in children with gastroesophageal reflux and congenital heart disease*,” S. Kuwata et al. showed that duodenal tube feeding improves the weight gain of infants with gastroesophageal reflux who need treatment for congenital-heart-disease-associated heart failure.

In the paper entitled “*Changes in ghrelin-related factors in gastroesophageal reflux disease in rats*,” M. Nahata et al. examined gastrointestinal hormone profiles and functional changes in rats with GERD. The results suggest that aberrantly increased secretion of peripheral ghrelin and decreased ghrelin responsiveness may occur in GERD rats.

In the paper entitled “*Surgical management of pediatric gastroesophageal reflux disease*,” H. T. Jackson and T. D. Kane review the clinical presentation of GERD in pediatric population and discuss the options for surgical management and outcome in these patients.

In the paper entitled “*Current advances in the diagnosis and treatment of nonerosive reflux disease*,” C. L. Chen and P. I. Hsu, review the literature about the pathogenesis, natural history, diagnosis and treatment of NERD. The authors suggest that a combination of 24-hour esophageal impedance and pH monitoring is indicated to differentiate acid-reflux-related NERD, weakly acid reflux-related NERD (hypersensitive esophagus), nonacid-reflux-related NERD, and functional heartburn in patients with poor response to appropriate PPI treatment.

In the paper entitled “*Antireflux endoluminal therapies: past and present*,” K. C. Yew et al. and S.-K. Chuah review, highlight, and discuss three commonly employed antireflux endoluminal procedures: fundoplication or suturing techniques (EndoCinch, NDO, EsophyX), intramural injection or implant techniques (enhancing LES volume and/or strengthening compliance of the LES-EnteryX, Gatekeeper), and radiofrequency ablation of lower esophageal sphincter and cardia (the Stretta system).

*Ping-I Hsu  
Nayoung Kim  
Khean Lee Goh  
Deng-Chyang Wu*

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## Review Article

# Stretta Radiofrequency Treatment for GERD: A Safe and Effective Modality

Mark Franciosa,<sup>1</sup> George Triadafilopoulos,<sup>2</sup> and Hiroshi Mashimo<sup>1</sup>

<sup>1</sup> Center for Swallowing and Motility Disorders, VA Boston Healthcare System, Harvard Medical School, Boston, MA 02132, USA

<sup>2</sup> Division of Gastroenterology and Hepatology, Stanford University School of Medicine, Stanford, CA 94040, USA

Correspondence should be addressed to Hiroshi Mashimo; [hmarshimo@hms.harvard.edu](mailto:hmarshimo@hms.harvard.edu)

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Gastroesophageal reflux disease is one of the leading gastrointestinal disorders. Current treatments include lifestyle modifications, pharmacological therapies, surgical funduplications, and, more recently, endoscopic procedures. The rising concern of long-term side effects of the popular proton-pump inhibitors and the more recent evidence raising doubts about the durability of fundoplication have spurred reinterest in endoscopic procedures to treat reflux disorders. In the aftermath of several innovative antireflux procedures that were introduced and failed clinically or financially over the past decade, there is lingering confusion regarding the merits of the presently available interventions. This paper focuses on one endoscopic procedure, Stretta, which now enjoys the longest experience, a recent meta-analysis, and robust data supporting its safety, efficacy, and durability. Stretta reduces esophageal acid exposure, decreases the frequency of transient lower esophageal relaxation, increases patient satisfaction, decreases medication use, and improves quality of life. As such, this procedure remains a valuable nonsurgical treatment option in the management of gastroesophageal reflux disease.

## 1. The Burden of Gastroesophageal Reflux Disease

Gastroesophageal reflux disease (GERD) is the most common digestive disorder affecting one third of the population worldwide and resulting in 4 to 5 million physician visits annually. It results primarily from the loss of an effective antireflux barrier against the retrograde movement of gastric contents into the distal esophagus. The average incremental cost in the United States to an employer for an employee with GERD in 2007 was estimated to be \$ 3,355 per year including medical costs, prescription drug costs, and indirect costs such as absenteeism and disability [1]. Furthermore, a significant financial burden on medical care comes from hospital admissions due to acid-induced noncardiac chest pain. Uncontrolled GERD results in a significant reduction in quality and productivity at work. GERD is also a risk factor for esophageal adenocarcinoma that is becoming increasingly

prevalent and has the fastest rising incidence of any cancer [2]. The current treatment for GERD consists of lifestyle modifications, pharmacological therapies, endoscopic procedures, and surgical interventions. The initial management of GERD includes lifestyle modifications, such as elevating the head of the bed, dietary modifications, restricting alcohol, and managing obesity. Pharmacological management typically consists of the use of H<sub>2</sub> blockers and, in most cases, proton-pump inhibitors (PPIs). Although medical therapy with PPIs is effective in most patients, there are increasing concerns regarding the long-term use of these drugs. These include interaction with a number of cardiac medications such as clopidogrel [3], association with osteoporotic fractures [4], hospital-acquired diarrhea and pneumonia, hypomagnesemia, and vitamin B12 malabsorption [5]. In addition, prolonged PPIs use has been associated with chronic atrophic gastritis in patients infected with *H. pylori* [6]. In the recent years, a significant number of patients with GERD are found

to be refractory to PPIs therapy despite even twice daily use of these drugs [7]. Surgical options for GERD also have their limitations including increased costs, hospitalization, up to 10% complication rate, and 28-day recovery [8]. Furthermore, the durability and side effects of fundoplication have fallen short of expectations. Recent 5-year data from the LOTUS trial suggests that 15%–20% of those who have undergone fundoplication may have GERD symptoms [9].

## 2. Advent of Nonsurgical Antireflux Devices

Since the early 2000's, several devices have been developed for the endoscopic treatment of GERD, using approaches such as sewing, transmural fasteners, endoscopic staplers, and thermal treatment using radiofrequency energy. Other devices involving injection, Enteryx (Boston Scientific, Boston, MA, USA) or implantation of foreign materials, Gatekeeper reflux repair system (Medtronic, Inc., Minneapolis, MN, USA) at the esophageal junction are no longer used. Devices that are currently commercially available for the endoscopic treatment of GERD in the United States include the following: EndoCinch (C. R. Bard, Inc., Murray Hill, NJ, USA); EsophyX (EndoGastric Solutions, Redwood City, CA, USA); Stretta (Mederi Therapeutics, Greenwich, CT, USA); and SRS Endoscope (Medigus, Omer, Israel). These are summarized in Table 1. Of these, Stretta, which applies radiofrequency energy to the lower esophageal sphincter (LES), has the longest experience in the treatment of GERD.

## 3. What Is Stretta?

The Stretta procedure involves the application of controlled radiofrequency (RF) energy to the LES region. The procedure, approved by the Food and Drug Administration in the United States in 2000, uses a flexible catheter with a balloon-basket assembly and nickel-titanium needle electrodes to deliver the radiofrequency energy into the esophageal wall and LES complex, while irrigating the overlying mucosa to prevent heat injury. Figure 1 illustrates the established mechanisms of action of Stretta.

Initial animal studies used porcine and canine models and showed a thickening of the LES, decreased transient lower esophageal relaxations (TLESRs), and decreased reflux events [10]. Multiple studies have demonstrated the safety and efficacy of the Stretta procedure for GERD therapy. Some studies had mixed results of its effectiveness and durability [11]. Despite four randomized clinical trials, more than 60 prospective trials and more than 800 patients followed post-Stretta procedure for 12 to 48 months, and there remain unanswered questions, overstated myths, and underappreciated realities about options in management of GERD. Such questions include whether PPIs are truly effective and safe, whether Stretta causes a stricture or neurolysis of the LES, whether Stretta effectively decreases acid exposure and improves symptoms and quality of life, and whether the improvements are durable over time. In this paper we address these questions and conclude that Stretta is a safe and effective

alternative to medical management or surgical management in selected patients.

## 4. Myths about Stretta

**4.1. Myth: Proton-Pump Inhibitors Effectively Control Symptoms in All Patients with GERD.** PPIs comprise a class of drugs widely used for the treatment of GERD. Their mechanism of action involves inhibition of the H-K ATPase enzyme that is present in gastric mucosal parietal cells. This enzyme is responsible for the secretion of hydrogen ions in exchange for potassium in the gastric lumen, and its inhibition decreases gastric acidity. First introduced in the late 1980's, PPIs were the most potent inhibitors of gastric acid secretion available, with efficacy superior to histamine-2 receptor antagonists. Because they effectively alleviate gastric-peptic symptoms and facilitate healing of inflamed or ulcerated mucosa, current guidelines recommend their use for the treatment of GERD. PPIs are also well tolerated, with side effects occurring at a rate of 1%–3% and with no significant differences among the various agents. Such side effects most commonly include headaches, nausea, abdominal pain, constipation, flatulence, diarrhea, rash, and dizziness. However, over the past decade, an increasing number of studies has shown that GERD symptom control is not as optimal as originally thought and marketed. A post hoc analysis of 5,794 patients from four randomized double-blind studies revealed that partial heartburn relief was experienced with the use of PPIs in 19.9% of patients with nonerosive reflux disease and in 14% of patients with reflux esophagitis [7]. Another study reported that only 61% of patients on PPIs with nonerosive esophageal reflux disease experienced resolution of heartburn [12].

**4.2. Myth: PPIs Use Is Safe.** Over the past decade, several potential adverse effects of long-term PPIs use had generated great concerns: B12 deficiency; iron deficiency; hypomagnesemia; increased susceptibility to pneumonia; enteric infections; fractures; hypergastrinemia; and drug-drug interactions [4]. This has led many patients with GERD either to self-discontinue therapy resulting in symptomatic recurrence or to solicit alternative methods to control their symptoms. Miyamoto and colleagues followed a cohort of 44 patients over 5 years and found that only 77% had improvement in their reflux symptoms [13]. Lundell and colleagues followed a cohort of 53 patients randomized to PPIs versus fundoplication; only 45% had continuous remission up to 12 years after randomization to the PPIs arm [14].

**4.3. Myth: Fundoplication Effectively Controls Reflux Symptoms.** Fundoplication as a means of controlling GERD symptoms over a sustained period of time has shown poor results. Lundell and colleagues followed a cohort of 144 patients for 7 years after fundoplication examining for recurrence of GERD symptoms and the need to resume medical management of reflux symptoms. They found that 34% had symptomatic relapse, and many of them required medical management [15]. Smith and colleagues followed a cohort of 1892 patients for 10 years post fundoplication and found that 17% had

TABLE 1: Overview of treatments for GERD.

Procedures	Anesthesia	Cost	Number of cases worldwide	Years of experience	Number of centers using the device	FDA-reported adverse events
Stretta	Conscious sedation	\$2000–3,500 per case	15,000	13	125	29
EsophyX	General anesthesia	\$7,000 per case	11,000	7	200	2
Medigus	General anesthesia	\$3,200 per case	>100	2	2	0
Linx	General anesthesia	\$12,000 per case	1000	5	70	0

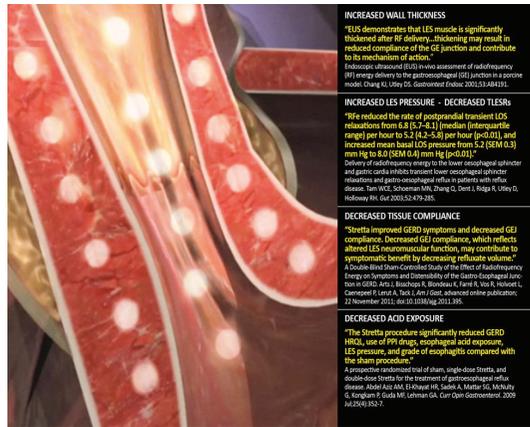


FIGURE 1: Stretta radiofrequency treatment mechanism of action (with the permission of Mederi Therapeutics, copyright 2013).

resumed using antisecretory medications [16]. Spechler and colleagues followed a cohort of 38 patients for 10 years after fundoplication and found that 62% were using antisecretory medications [17]. Oelschlager and colleagues followed a cohort of 289 patients for 5 years and found that 61% of them were taking some forms of antacid [18].

**4.4. Myth: Stretta Causes Distal Esophageal Strictures.** Although the exact mechanism of action of Stretta in relieving symptoms of acid reflux is unknown, one potential mechanism is that it decreases the number of TLESRs [19]. The latest theory suggests that this is accomplished by a structural rearrangement of the smooth muscle and redistribution of the interstitial cells of Cajal in the smooth muscle of the LES [20]. Stretta was designed to minimize damage to the esophagus. The four-channel radiofrequency (RF) generator and catheter system delivers pure sine-wave energy (465 kHz, 2 to 5 watts per channel, and 80 volts maximum at 100 to 800 ohms). Each needle tip incorporates a thermocouple that automatically modulates power output to maintain a desired target (muscle) tissue temperature. Maintaining lesion temperatures below 50°C minimizes the collateral tissue damage due to vaporization and high impedance values. Temperature is similarly monitored with a thermocouple at each needle base, and power delivery ceases if the mucosal temperature exceeds 50°C or if impedance exceeds 1000 mOhms [19]. Maintaining tight temperature control prevents mucosal damage to the distal esophagus and gastroesophageal junction thus preventing stricture

formation. A recent double-blind sham-controlled study of 22 patients showed that administration of sildenafil, an esophageal smooth muscle relaxant, normalized the gastroesophageal junction compliance to pre-Stretta levels, arguing against GE junction fibrosis as an underlying mechanism [19].

**4.5. Myth: Stretta Causes Neurolysis in the Distal Esophagus.** DiBaise and colleagues followed a cohort of 18 patients 6 months after Stretta and found no adverse effects on abdominal vagal function and no significant changes in any esophageal motility parameter; however, a trend was noted toward a reduction in the number of TLESRs induced by gastric air distension (3.5/h versus 1.0/h;  $P = 0.13$ ). No detrimental effects on peristalsis or swallow-induced LES relaxation pressure were seen [21]. Arts and colleagues also followed a cohort of 13 patients for 6 months after Stretta and found that esophageal peristalsis (low-amplitude peristalsis in the same three patients), resting LES pressure ( $18.2 \pm 2.0$  mm Hg; NS), and swallow-induced relaxations were not significantly altered by the radiofrequency energy delivery procedure, which also argues against the theory of neurolysis [22].

**4.6. Myth: Stretta Does Not Decrease Esophageal Acid Exposure.** Several studies have shown a decrease in esophageal acid exposure after Stretta. Arts and colleagues followed a cohort of 13 patients over 6 months, and all patients underwent repeat pH monitoring 6 months after the procedure. One measurement was technically inadequate and not interpretable. In the evaluable patients, esophageal pH monitoring was significantly improved, from  $11.6\% \pm 1.6\%$  to  $8.5\% \pm 1.8\%$  of the time at pH < 4 ( $P < 0.05$ ) (Figure 2). Normalization of the pH monitoring (<4% of the time at pH < 4) occurred in only three patients. The DeMeester score showed a similar improvement, from  $46.8 \pm 7.3$  to  $35.6 \pm 6.7$  ( $P = 0.01$ ) [21]. Aziz and colleagues showed similar results from their prospective randomized sham study of 36 patients, which showed significant reduction in esophageal acid exposure [23]. Not all studies have come to the same conclusion. DiBaise and colleagues followed a cohort of 18 patients after Stretta for 6 months and found that there were no adverse effects on vagal function and esophageal motility. There were an improvement in symptoms, a decreased antacid use, and decreased TLESRs, but no significant difference in esophageal acid exposure [21]. Even though decrease in acid exposure was not achieved in this study, Stretta did

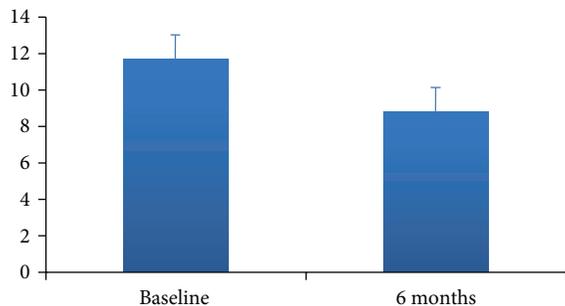


FIGURE 2: Acid exposure (% pH < 4.0) before and after Stretta.

accomplish the primary goals of GERD treatment which are to improve symptoms, improve quality of life, and decrease medication use. Although this study did not show decreased acid exposure, there are multiple other studies that did show a decrease, and it is important to look at the entire body of research showing, in many cases, improvement in acid exposure.

The recently published meta-analysis by Perry and colleagues evaluated 18 studies and 1441 patients and showed a significant reduction in esophageal acid exposure after Stretta. Preprocedure and postprocedure esophageal pH studies were documented in 11 of the 20 studies. The DeMeester score improved from  $44.37 \pm 93$  before Stretta to  $28.53 \pm 33.4$  after Stretta over an average period of 13.1 months in 267 patients across 7 studies ( $P = 0.0074$ ). The esophageal acid exposure was reported in 11 studies comprising of 364 patients over a mean follow-up period of 11.9 months. Esophageal acid exposure decreased from a mean of  $10.29\% \pm 17.8\%$  to  $6.51\% \pm 12.5\%$  ( $P = 0.0003$ ) [11].

#### 4.7. Myth: Stretta Relieves GERD Symptoms by Placebo Effect.

Due to the lack of certainty around the mechanism by which Stretta relieves GERD symptoms, there is a misconception that Stretta works by placebo effect. Arts and colleagues performed a double-blind sham-controlled study showing that Stretta decreases LES compliance, which likely mitigates inappropriate LES relaxations, the most common underlying cause of GERD. This study also showed that there was a significant improvement in symptoms as compared with the patients who received the sham procedure [19]. Further evidences that Stretta does not work by placebo effect are the studies showing decreased esophageal acid exposure after Stretta [22, 23]; see Table 2 for the summary of the myths about Stretta.

## 5. Realities of Stretta

**5.1. Reality: Stretta Improves Quality of Life and Patient Satisfaction.** There have been numerous studies showing that patients treated with Stretta have a significant improvement in quality of life. In the meta-analysis by Perry, 18 studies containing 433 patients evaluated the effect of treatment on patient quality of life (QoL) using the GERD-HRQL scale with an average follow-up interval of 19.8 months. The QoL

scores improved from  $26.11 \pm 27.2$  at baseline to  $9.25 \pm 23.7$  after treatment ( $P = 0.0001$ ). QoL scores were collected from 4 studies comprising 250 patients and were improved from  $3.3 \pm 5.9$  to  $4.97 \pm 4.9$  at a mean follow-up interval of 25.2 months ( $P = 0.001$ ). SF-36 was utilized to assess global QoL of the patient population in 6 studies. A total of 299 patients responded to the SF-36 physical form, during a mean follow-up period of 9.5 months, demonstrating an improvement from  $36.45 \pm 51.6$  at baseline to  $46.12 \pm 61.9$  after procedure ( $P = 0.0001$ ). Two hundred sixty-four patients in 5 of the 6 studies responded to the SF-36 mental form demonstrating improvement from  $46.79 \pm 20.5$  to  $55.16 \pm 17.6$  at 10-month followup ( $P = 0.0015$ ) [11] (Figure 3).

#### 5.2. Reality: Stretta Decreases Acid Reflux Symptoms and Medication Use.

There have been several studies showing a significant decrease in medication use after Stretta. Triadafilopoulos and colleagues conducted a nonrandomized, prospective, and multicenter study that included 118 patients treated with Stretta for GERD. Follow-up information was available for 94 patients (80%) at 12 months; the proportion of patients requiring PPIs fell from 88% to 30%. There was also an improvement in quality of life scores and reduction in esophageal acid exposure [20]. In another trial by Liu and colleagues of 90 patients with nonerosive or mildly erosive disease, the onset of GERD symptom relief after Stretta was less than two months in 70.0% and two-to-six months in 16.7%, while there was a significant improvement in GERD symptoms and patient satisfaction (Figure 4). Medication usage decreased significantly from 100% of patients on PPIs therapy at baseline to 76.7% of patients showing elimination of medication use or only as-needed use of antacids/H2-receptor antagonists at 12 months [24]. Dughera and colleagues reported similar results in 48-month follow-up data for 56 out of 69 patients who were treated with Stretta. RF treatment significantly improved heartburn scores, GERD-related quality of life scores, and general quality of life scores at 24 and 48 months in 52 out of 56 patients (92.8%). At 48 months, 41 out of 56 patients (72.3%) were completely off PPIs (Figure 5). Morbidity was minimal, except for one patient who developed transient gastroparesis [25].

#### 5.3. Reality: Stretta Is Safe.

The recently published meta-analysis by Perry revealed that the most common complications encountered after the Stretta procedure were gastroparesis and erosive esophagitis. These are known to be transient and reversible. Early reports of esophageal perforations were attributed to operators' inexperience, and no such grave complications have been reported since then [10]. In a study of 77 patients who had the Stretta procedure, none had esophageal perforation, dysphasia, or severe gas bloating or stricture, documenting low complication rates for mild fever (2/24:8%), pneumonia (1/24:4%), transient dysphasia (3/24:12.5%), abdominal pain (2/24:8%) and 0% mortality [26]. Complication rates compare favorably with those of surgical interventions that appear to be around 4%, for laparoscopic procedures and 9% for open funduplications [27]. There have been only 29 adverse events for more

TABLE 2: Summary of myths and realities concerning GERD treatment.

Myths	Realities
Proton-pump inhibitors effectively control symptoms in all patients with GERD.	Stretta improves quality of life and patient satisfaction.
Proton-pump inhibitor use is safe.	Stretta decreases acid reflux symptoms and medication use.
Fundoplication effectively controls reflux symptoms.	Stretta is not for every patient with GERD.
Stretta causes distal esophageal strictures.	Stretta is safe.
Stretta causes neurolysis in the distal esophagus.	Stretta is durable.
Stretta does not decrease esophageal acid exposure.	Stretta improves gastric emptying.
Stretta works by placebo effect.	Stretta has limitations.

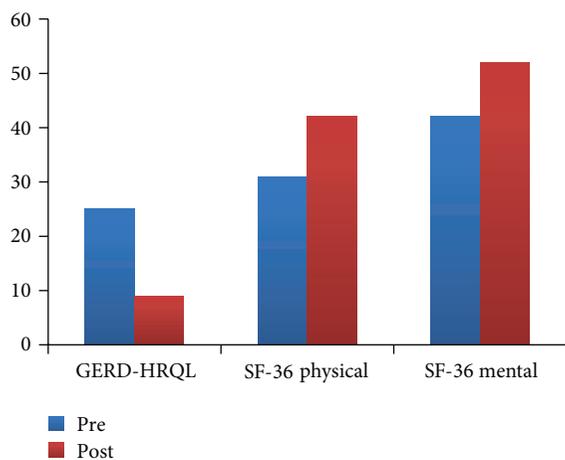


FIGURE 3: Scores before and after Stretta.

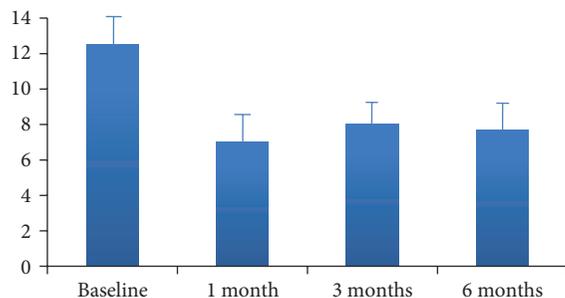


FIGURE 4: Reflux symptoms 6 months after Stretta.

than 15,000 preformed procedures reported to the FDA with the last being in 2005. There have been no adverse events reported since the latest upgrades of the Stretta device in 2005. The upgrades include more sensitive temperature controls, easier user interface, and newer ablation prongs.

**5.4. Reality: Stretta Is Durable.** There have been several long-term studies examining the durability of Stretta. One of the longest follow-up studies has been that by Noar and colleagues who showed that, in 109 patients with 48 months of followup, 75% of patients showed statistically significant reduction in PPIs usage, and there were significant

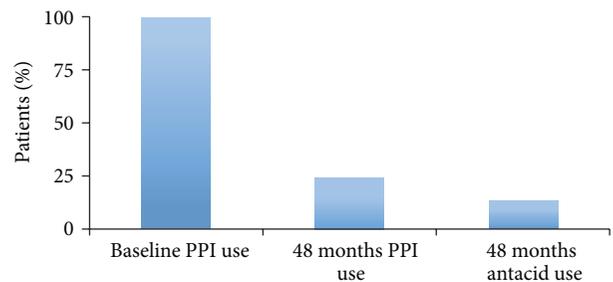


FIGURE 5: PPI and antacid use 48 months after Stretta.

improvements in patient satisfaction and heartburn scores [28]. Another study by Reymunde and colleagues followed a cohort of 83 patients for 48 months and found statistically significant improvement in GERD symptom scores and GERD-QoL scores, besides reporting that daily medication use was needed by only 13.6% of patients at 48 months, compared with 100% prior to treatment [29] (Figure 6). Recently, Dughera reported on 56 patients who also reached 48 months of followup and had significantly improved heartburn scores, GERD-specific QoL scores, and general QoL scores at 24 and 48 months in 52 (93%) of patients. At 48 months, 41 patients (72%) were completely off PPIs [25]. At 8 years, 60% of available patients were still not using PPIs [30]. This compares favorably with outcomes after fundoplication, showing that nearly 60% undergoing surgery were back on PPIs after 8 years.

**5.5. Reality: Stretta Improves Gastric Emptying.** Growing clinical evidence shows that delayed gastric emptying (gastroparesis) may be a factor associated with severe reflux, dyspepsia, or both. Gastroparesis, concomitant in 25% of patients with gastroesophageal reflux disease (GERD), has been shown to improve after Stretta. Radiofrequency treatment for GERD may potentially correct GERD-associated gastroparesis and resultant reflux failures despite the twice daily use of PPIs. Noar and colleagues showed that at 6 months after Stretta procedure gastric emptying scores had improved significantly, with the percentage of solid food emptied at 90 min improving from 41% to 66% ( $P < 0.0001$ ) and at 120 min improving from 55% to 84%. Significant improvements were seen at all time intervals. Overall, 23

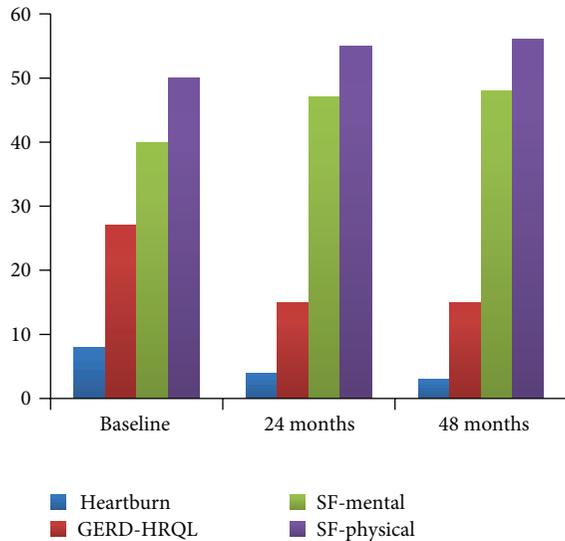


FIGURE 6: Symptoms and quality of life after Stretta.

patients (74%) experienced normalization of gastric emptying, and 4 patients improved but remained abnormal. Four patients showed no improvement on their gastric emptying scans, with one patient electing to undergo a Nissen procedure. All of the patients had a 1-year symptom follow-up assessment, which showed significant improvements in GERD-related quality of life, dyspepsia, and heartburn scores [31].

**5.6. Reality: Stretta Has Limitations.** One of the limitations of Stretta is that it has not proven to be cost effective. In a study by Comay et al., which followed a cohort of patients for 5 years after being randomized to either once daily PPIs therapy, fundoplication, or Stretta, this cohort was evaluated for quality-adjusted life years, symptom-free months, and cost effectiveness. Their results showed that the PPIs procedure was the most cost effective strategy depending on the price of omeprazole per pill. If the price of omeprazole was over \$2.00 per pill, then Stretta was deemed the most cost-effective of the three strategies. The costs in this study were reported in Canadian dollars and based on costs in the Canadian health system. The estimated cost in this study of 5 years of PPIs use was \$2394.10, the cost of Stretta was \$3,239.30, and the cost of fundoplication was \$7394.70 [32]. There is great variability in the cost of PPIs in the United States. At the time of this publication, the average retail price per pill in one major pharmacy chain was for \$2.63 per pill omeprazole, for \$4 per pill pantoprazole, and for \$8.30 per pill esomeprazole. The hidden cost the patient must also take into consideration is the increasing number of side effects of PPIs that are being reported and the increasing appreciation of treatment failures [12]. Although Stretta has been associated with 29 complications in over 15,000 cases, including 5 esophageal perforations early in its launch, no serious adverse events have been experienced since the modified generator and catheter in 2011 under Mederi Therapeutics were used.

Gastroparesis is a side effect of Stretta. Dughera and colleagues found that only 1 out of 56 patients treated with Stretta developed gastroparesis, and this resolved in 8 weeks [25]. Noar and colleagues showed that Stretta improved gastroparesis in a study where they followed a cohort of 31 patients with gastroparesis 6 months after Stretta and found that 74% of patients have normalization of gastric emptying [31]. There have been more frequent cases of postsurgical gastroparesis that develops after surgical fundoplication for GERD. It is estimated that 4% to 40% of patients who undergo laparoscopic fundoplication develop intraoperative vagal damage to some degree [33].

**5.7. Reality: Stretta Is Not for Every Patient with GERD.** Stretta is ideal for patients with heartburn or regurgitation, patients who have adequate esophageal peristalsis, who have unsatisfactory GERD control with PPIs therapy, patients who have 24-hour pH monitoring demonstrating pathologic acid reflux, and patients who have nonerosive reflux disease or grade A or B esophagitis. The patients who are not considered good candidates for the Stretta procedure include those patients with a greater than 2 cm long hiatal hernia, patients who have significant dysphagia, patients who have grade C or D esophagitis, and patients who have inadequate esophageal peristalsis and incomplete LES relaxation with swallowing [34]. Thus, careful patient selection is important to assure benefit from this as well as other comparable procedures; see Table 2 for the summary of the realities of Stretta.

## 6. Conclusions

In this paper, several randomized and prospective long-term studies have been presented that address concerns about the safety, tolerability, efficacy, and durability of Stretta that may make Stretta a more desirable treatment option than chronic PPI use or fundoplication in selected patients.

## Conflict of Interests

Dr. Franciosa, Dr. Triadafilopoulos, and Dr. Mashimo do not have any conflict of interests to report with this paper.

## Authors' Contribution

M. Franciosa, G. Triadafilopoulos, H. Mashimo all contributed equally to this work.

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## Clinical Study

# The Frequencies of Gastroesophageal and Extragastroesophageal Symptoms in Patients with Mild Erosive Esophagitis, Severe Erosive Esophagitis, and Barrett's Esophagus in Taiwan

Sung-Shuo Kao,<sup>1</sup> Wen-Chih Chen,<sup>1</sup> Ping-I Hsu,<sup>1,2</sup> Seng-Kee Chuah,<sup>3</sup> Ching-Liang Lu,<sup>4</sup> Kwok-Hung Lai,<sup>1,5</sup> Feng-Woei Tsai,<sup>1</sup> Chun-Chao Chang,<sup>6</sup> and Wei-Chen Tai<sup>3</sup>

<sup>1</sup> Division of Gastroenterology, Department of Internal Medicine, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan

<sup>2</sup> National Yang-Ming University, Taipei, Taiwan

<sup>3</sup> Division of Hepato-Gastroenterology, Department of Internal Medicine, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung City 833, Taiwan

<sup>4</sup> Division of Gastroenterology, Department of Internal Medicine, Taipei Veterans General Hospital, Taipei, Taiwan

<sup>5</sup> Department of Medical Education and Research, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan

<sup>6</sup> Department of General Medicine, School of Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan

Correspondence should be addressed to Wei-Chen Tai; [luketai1019@gmail.com](mailto:luketai1019@gmail.com)

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**Background.** Gastroesophageal reflux disease (GERD) may present with gastroesophageal and extraesophageal symptoms. Currently, the frequencies of gastroesophageal and extragastroesophageal symptoms in Asian patients with different categories of GERD remain unclear. **Aim.** To investigate the frequencies of gastroesophageal and extragastroesophageal symptoms in patients with mild erosive esophagitis, severe erosive esophagitis, and Barrett's esophagus of GERD. **Methods.** The symptoms of symptomatic subjects with (1) Los Angeles grade A/B erosive esophagitis, (2) Los Angeles grade C/D erosive esophagitis, and (3) Barrett's esophagus proven by endoscopy were prospectively assessed by a standard questionnaire for gastroesophageal and extragastroesophageal symptoms. The frequencies of the symptoms were compared by Chi-square test. **Result.** Six hundred and twenty-five patients (LA grade A/B: 534 patients; LA grade C/D: 37 patients; Barrett's esophagus: 54 patients) were assessed for gastroesophageal and extragastroesophageal symptoms. Patients with Los Angeles grade A/B erosive esophagitis had higher frequencies of symptoms including epigastric pain, epigastric fullness, dysphagia, and throat cleaning than patients with Los Angeles grade C/D erosive esophagitis. Patients with Los Angeles grade A/B erosive esophagitis also had higher frequencies of symptoms including acid regurgitation, epigastric acidity, regurgitation of food, nausea, vomiting, epigastric fullness, dysphagia, foreign body sensation of throat, throat cleaning, and cough than patients with Barrett's esophagus. **Conclusion.** The frequencies of some esophageal and extraesophageal symptoms in patients with Los Angeles grade A/B erosive esophagitis were higher than those in patients with Los Angeles grade C/D erosive esophagitis and Barrett's esophagus. The causes of different symptom profiles in different categories of GERD patients merit further investigations.

## 1. Introduction

The Montreal Definition and Classification of Gastroesophageal Reflux Disease defines GERD as a condition which develops when the reflux of stomach contents causes troublesome symptoms and/or complications [1]. Gastroesophageal reflux occurs when there is a transient decrease in tension in the lower esophageal sphincter, allowing gastric contents

to leak into the esophagus [2]. In most people with GERD, gastric juice reflux causes heartburn, as a painful or burning sensation in the esophagus, but regurgitation of digestive juices is also common [3]. Other than two classic reflux symptoms above, dysphagia is reported by more than 30% of individuals with GERD [4]. Less common symptoms associated with GERD include water brash, burping, hiccups,

nausea, and vomiting [5]. Gastroesophageal reflux may also be associated with manifestations affecting a wide range of extraesophageal tissues and organ systems. In the large German ProGERD study of patients presenting with heartburn, nearly one-third had extraesophageal reflux disorders at baseline. Common extraesophageal manifestations in GERD patients were chronic cough, laryngeal disorders, and asthma [6]. Some patients with GERD, however, are asymptomatic [7]. This is particularly true in the older adults, perhaps because of decreased acidity of the reflux material in some or decreased pain perception in others [8].

Although patients with Los Angeles grade C/D erosive esophagitis and Barrett's esophagus have more frequencies of acidic reflux episodes than those with LA grade A/B erosive esophagitis [9], the intensity and frequency of reflux symptoms are poor predictors of the presence of severe esophagitis. In a study investigating over 4000 patients with esophagitis, the percentage of patients with moderate or severe heartburn was comparable across all grades of disease [10]. Another study comparing the spectrum of heartburn severity in those with and without underlying esophagitis is similar, with over 60% of patients in both groups experiencing moderate or severe heartburn [11]. Additionally, an international, multicenter study revealed that the gastrointestinal symptom patterns were similar in patients with erosive and nonerosive esophagitis [12]. Another Chinese study also pointed out symptom resolution not predicting healing of erosive esophagitis [13]. These results may reflect the phenomenon that acid exposure is related to the severity of esophagitis but does not completely correlate with the severity of symptoms.

Barrett's esophagus, the normal squamous epithelium in the distal esophagus replaced by columnar epithelium, is considered one of the most important complications of gastroesophageal reflux disease [14]. There is controversy as to whether GERD exists as a spectrum of disease severity or as a categorical disease in three distinct groups, including Barrett's esophagus. In a prevalence study in Sweden, Barrett's esophagus was found in 1.6% of the general adult population, of which 56.3% had reflux symptoms [15]. Many patients with short-segment Barrett's esophagus have no GERD symptoms and no endoscopic signs of esophagitis in another study [16]. Bredenoord et al. discovered that patients with LA grade C/D reflux esophagitis and those with Barrett's esophagus have high total number of reflux episodes, but patients with LA grade C/D have higher percentage of reflux episodes reaching the proximal esophagus than those with Barrett's esophagus [9]. This might explain their low sensitivity to reflux in patients with Barrett's esophagus.

Past studies regarding the prevalence of GERD symptoms were more focused on heartburn and acid regurgitation. There were no studies comparing the frequencies of all gastroesophageal and extragastroesophageal GERD symptoms in different severity of erosive esophagitis and Barrett's esophagus. In addition, the independent factors related to the development of extraesophageal symptoms remain unanswered. The aim of this study was therefore to compare the prevalence of gastroesophageal and extragastroesophageal symptoms in patients with various degrees of esophagitis and

Barrett's esophagus. Special attention was also paid to the clinical factors related to the presence of extragastroesophageal symptoms.

## 2. Patients and Methods

**2.1. Patients.** Consecutive symptomatic patients with erosive esophagitis or histologically confirmed Barrett's esophagus diagnosed during endoscopy at Kaohsiung Veterans General Hospital and Kaohsiung Chang Gung Memorial Hospital of Taiwan between 2008 and 2012 were recruited. Subjects enrolled were further divided into three categories according to endoscopic findings: (1) mild erosive esophagitis: LA grade A/B erosive esophagitis, (2) severe erosive esophagitis: LA grade C/D erosive esophagitis, and (3) Barrett's esophagus. Patients were excluded if they had histories of (1) younger than 15 years old, (2) gastrointestinal malignancies, (3) pregnancy, (4) acute stress conditions (including sepsis, acute renal failure), (5) previous gastric surgery, (6) equivocal diagnosis of erosive esophagitis, and (7) taking proton pump inhibitor (PPI) and H2 receptor antagonist in the preceding 2 weeks before endoscopy. Baseline demographic data, smoking and alcohol histories were collected.

**2.2. Study Design.** At the clinic visit, patients with acid regurgitation and/or heartburn were invited to receive panendoscopy surveillance for esophagitis or Barrett's esophagus. Patients with erosive esophagitis or Barrett's esophagus were prospectively assessed by a standard questionnaire for gastroesophageal and extragastroesophageal symptoms. All participants were asked about their consumption of H2-receptor antagonists and PPI over the past 2 weeks and about their tobacco, alcohol, coffee, and tea consumption. Venous blood samples for fasting glucose, cholesterol, and triglyceride were also taken. *Helicobacter pylori* infection was determined by the histology of gastric mucosa taken during endoscopy.

**2.2.1. Definitions of Barrett's Esophagus and Erosive Esophagitis.** At endoscopy, esophageal mucosal breaks (esophagitis) were graded from A to D according to the LA classification system [17, 18]. Esophageal biopsy was taken when salmon-pink mucosal projections from cardia were identified during endoscopy [19–21]. The diagnosis of Barrett's esophagus was confirmed by the presence of gastric or intestinal metaplasia in the esophageal biopsy specimens [22, 23].

**2.2.2. Questionnaire.** A complete medical history and demographic data were obtained from each patient, including age, sex, body mass index (BMI), medical histories, and histories of smoking, alcohol, coffee, tea, spice, and sweets consumption. The history of gastroesophageal symptoms (including acid regurgitation, heartburn, epigastric acidity, bleeding, chest pain, regurgitation of food, nausea, vomiting, hiccup, epigastric pain, epigastric fullness, and dysphagia) and extraesophageal symptoms (including throat foreign body sensation, hoarseness, throat cleaning, cough, sore throat, and bad breath) were taken.

TABLE 1: Demographic data of patients with mild erosive esophagitis, severe esophagitis, and Barrett's esophagus.

Characteristics	Mild erosive esophagitis (LA grade A/B)	Severe erosive esophagitis (LA grade C/D)	Barrett's esophagus
Patient number	N = 534	N = 37	N = 54
Age (yr) (mean ± SD)	51.05 ± 12.34	56.89 ± 12.83*	51.26 ± 11.66 <sup>#</sup>
Gender (male)	300/534 (56.2%)	32/37 (86.5%)*	38/54 (70.4%)
Metabolic syndrome	144/458 (31.4%)	15/35 (42.9%)	15/46 (32.6%)
Hiatal hernia	120/532 (22.6%)	26/37 (70.3%)*	15/54 (27.8%) <sup>#</sup>

\*  $P < 0.05$  compared with esophagitis A/B.<sup>#</sup>  $P < 0.05$  compared with esophagitis C/D.

TABLE 2: Frequencies of gastroesophageal symptoms in patients with mild erosive esophagitis, severe erosive esophagitis, and Barrett's esophagus.

Symptoms	Mild erosive esophagitis (LA grade A/B)	Severe erosive esophagitis (LA grade C/D)	Barrett's esophagus
Acid regurgitation	461/534 (86.3%)	33/37 (89.2%)	36/54 (66.7%)**
Heartburn	312/534 (58.4%)	18/37 (48.6%)	27/54 (50.0%)
Epigastric acidity	380/534 (71.2%)	21/37 (56.8%)	28/54 (51.9%)*
Esophageal bleeding	11/533 (2.1%)	2/37 (5.4%)	0/54 (0.0%)
Chest pain	177/466 (38.0%)	13/37 (35.1%)	14/54 (25.9%)
Regurgitation of food	152/466 (32.6%)	7/37 (18.9%)	10/54 (18.5%)*
Nausea	162/534 (30.3%)	7/37 (18.9%)	9/54 (16.7%)*
Vomiting	79/534 (14.8%)	7/37 (18.9%)	1/54 (1.9%)**
Hiccup	289/534 (54.1%)	16/37 (43.2%)	26/54 (48.1%)
Epigastric pain	269/534 (50.4%)	8/36 (22.2%)*	20/54 (37.0%)
Epigastric fullness	347/534 (65.0%)	16/37 (43.2%)*	27/54 (50.0%)*
Dysphagia	98/534 (18.4%)	2/37 (5.4%)*	4/54 (7.4%)*

\*  $P < 0.05$  compared with esophagitis A/B.<sup>#</sup>  $P < 0.05$  compared with esophagitis C/D.

2.3. *Statistics.* Statistical analysis was performed using the Statistical Program for Social Sciences (SPSS 19.0 for windows). Univariate analysis was performed by Student's  $t$ -test for continuous variables and  $\chi^2$  test was used for categorical variables. Backward stepwise conditional binary logistic regression analysis was performed to determine independent risk factors of certain extragastric symptoms.  $P < 0.05$  was considered statistically significant and all reported  $P$  values were two-sided.

### 3. Results

3.1. *Study Population.* Six hundred and twenty-five patients with erosive esophagitis or Barrett's esophagus were enrolled in the study. The mean age of the patients was  $51.4 \pm 12.4$  years old, and 370 (59%) were males. They were categorized as mild erosive esophagitis (LA grade A/B;  $n = 534$ ), severe erosive esophagitis (LA grade C/D,  $n = 37$ ), and Barrett's esophagus ( $n = 54$ ). Data regarding the clinical characteristics of patients at entry are summarized in (Table 1). Patients with LA grade C/D erosive esophagitis had higher mean age ( $56.89 \pm 12.83$  versus  $51.05 \pm 12.34$ ), more male predominance

(86.5% versus 56.2%), and more underlying hiatal hernia (70.3% versus 22.6%) than patients with LA grade A/B erosive esophagitis (Table 1). Additionally, they also had higher mean age ( $56.89 \pm 12.83$  versus  $51.26 \pm 11.66$ ) and more underlying hiatal hernia (70.3% versus 27.8%) than patients with Barrett's esophagus.

3.2. *Frequencies of Gastroesophageal Symptoms in Different Categories of GERD.* Table 2 lists the frequencies of gastroesophageal symptoms in each group of GERD patients. Generally, patients with mild (Los Angeles grade A/B) erosive esophagitis had more gastroesophageal symptoms. Patients with mild erosive esophagitis had higher frequencies of epigastric pain (50.4% versus 22.2%;  $P = 0.001$ ), epigastric fullness (65.0% versus 43.2%;  $P = 0.008$ ), and dysphagia (18.4% versus 5.4%;  $P = 0.045$ ) than patients with severe erosive esophagitis. Patients with mild erosive esophagitis also had higher frequencies of acid regurgitation (86.3% versus 66.7%;  $P < 0.001$ ), epigastric acidity (71.2% versus 51.9%;  $P = 0.003$ ), regurgitation of food (32.6% versus 18.5%;  $P = 0.034$ ), nausea (30.3% versus 16.7%;  $P = 0.035$ ), vomiting (14.8% versus 1.9%;  $P = 0.008$ ), epigastric fullness (65.0%

TABLE 3: Frequencies of extragastroesophageal symptoms in patients with mild erosive esophagitis, severe erosive esophagitis, and Barrett's esophagus.

Symptoms	Mild erosive esophagitis (LA grade A/B)	Severe erosive esophagitis (LA grade C/D)	Barrett's esophagus
Foreign body sensation of throat	236/467 (50.5%)	13/37 (35.1%)	18/54 (33.3%)*
Hoarseness	164/534 (30.7%)	12/37 (32.4%)	11/54 (20.4%)
Throat cleaning	195/466 (41.8%)	8/37 (21.6%)*	14/54 (25.9%)*
Cough	147/534 (27.5%)	13/37 (35.1%)	8/54 (14.8%)*#
Sore throat	102/534 (19.1%)	6/37 (16.2%)	9/54 (16.7%)

\*  $P < 0.05$  compared with esophagitis A/B.

#  $P < 0.05$  compared with esophagitis C/D.

TABLE 4: Independent factors for extragastroesophageal symptoms in patients with mild erosive esophagitis, severe erosive esophagitis, and Barrett's esophagus.

Symptoms	Risk factors	Coefficient	Standard error	OR (95% CI)	$P$ value
Foreign body sensation	Esophagitis A/B	0.713	0.331	2.039 (1.067–3.899)	0.031
Throat cleaning	Esophagitis A/B	0.731	0.351	2.077 (1.044–4.133)	0.037
Cough	Esophagitis A/B	0.946	0.454	2.575 (1.058–6.272)	0.037
	Male gender	−0.481	0.204	0.618 (0.414–0.923)	0.019
Sore throat	Metabolic syndrome	−0.555	0.263	0.574 (0.343–0.960)	0.034
Hoarseness*	N/A	N/A	N/A	N/A	N/A

\* No single risk factor was identified contributing to the development of hoarseness.

versus 50.0%;  $P = 0.029$ ), and dysphagia (18.4% versus 7.4%;  $P = 0.043$ ) than patients with Barrett's esophagus. Additionally, patients with severe erosive esophagitis had higher frequency of acid regurgitation (89.2% versus 66.7%;  $P = 0.014$ ) and vomiting (18.9% versus 1.9%;  $P = 0.005$ ) than patients with Barrett's esophagus.

**3.3. Frequencies of Extragastroesophageal Symptoms in Different Categories of GERD.** Table 3 displays the frequencies of extragastroesophageal symptoms in each group of GERD patients. Patients with mild (Los Angeles grade A/B) erosive esophagitis had more frequent extragastroesophageal symptoms than the other two groups of patients. Patients with mild erosive esophagitis had higher frequency of throat cleaning (41.8% versus 21.6%;  $P = 0.016$ ) than patients with severe erosive esophagitis. Patients with mild erosive esophagitis also had higher frequency of foreign body sensation of throat (50.5% versus 33.3%;  $P = 0.017$ ), throat cleaning (41.8% versus 25.9%;  $P = 0.024$ ), and cough (27.5% versus 14.8%;  $P = 0.043$ ) than patients with Barrett's esophagus. In addition, cough was more frequent in patients with severe erosive esophagitis than patients with Barrett's esophagus (35.1% versus 14.8%;  $P = 0.024$ ).

**3.4. Factors Related to the Presence of Extragastroesophageal Symptoms.** Table 4 lists the independent factors of extragastroesophageal symptoms. We examined several possible variables for extragastroesophageal symptoms, such as age, gender, hiatal hernia, metabolic syndrome, and grade of esophagitis. The prevalence of foreign body sensation of throat was significantly higher in patients with mild erosive

esophagitis ( $P = 0.031$ , odds ratio (OR): 2.039, and 95% confidence interval (CI): 1.067–3.899) (Table 4). For throat cleaning, mild erosive esophagitis was still the only independent factor contributing to prevalence ( $P = 0.037$ , OR: 2.077, and 95% CI: 1.044–4.133) (Table 4). Additionally, mild erosive esophagitis was an independent risk factor for the presence of cough ( $P = 0.037$ , OR: 2.575, and 95% CI: 1.058–6.272), while male gender was a protective factor ( $P = 0.019$ , OR: 0.618, and 95% CI: 0.414–0.923) for cough. We also found that patients with metabolic syndrome have lower rates of the development of sore throat ( $P = 0.034$ , OR: 0.574, and 95% CI: 0.343–0.960).

## 4. Discussion

This study is the first work simultaneously investigating the differences in gastroesophageal and extragastroesophageal symptoms among various categories of GERD. We have demonstrated that patients with LA grade A/B erosive esophagitis had higher frequencies of gastroesophageal symptoms (epigastric pain, epigastric fullness, and dysphagia) and extragastroesophageal symptoms (throat cleaning) than patients with LA grade C/D erosive esophagitis. In addition, they also had higher frequencies of gastroesophageal symptoms (acid regurgitation, epigastric acidity, regurgitation of food, nausea, vomiting, epigastric fullness, and dysphagia) and extragastroesophageal symptoms (foreign body sensation of throat, throat cleaning, and cough) than patients with Barrett's esophagus.

Our findings were consistent with a previous study reporting that patients with Barrett's esophagus had less frequent

or less severe symptoms than patients with GERD [24]. Currently, the reasons for mild erosive esophagitis with more frequencies of gastroesophageal and extragastroesophageal symptoms remain unclear. Bredenoord et al., examining the episodes of all reflux, acid reflux, and weakly acid reflux in patients with different severity of GERD, showed that more reflux episodes were found in patients with more severe esophageal mucosal injury [9]. Another study also found that patients with erosive esophagitis had the longest duration of distal esophageal acid exposure than patients with nonerosive reflux disease and normal volunteers [25]. Therefore, the degree of acid exposure of esophagus cannot explain the findings in our study. Possible explanations for our findings include different esophageal sensitivity and different frequencies of laryngopharyngeal reflux in various categories of GERD. We suppose that the esophageal mucosa in patients with mild erosive esophagitis may be more sensitive to refluxate than patients with severe erosive esophagitis or Barrett's esophagus. Second, laryngopharyngeal reflux is different in each group of GERD patients. Bredenoord et al. reported that patients with Barrett's esophagus having fewer reflux episodes reached proximal esophagus when compared with patients of Los Angeles grade C/D erosive esophagitis [9]. The finding may explain lower frequency of extragastroesophageal symptoms in patients with Barrett's esophagus than in patients with severe erosive esophagitis.

In this study, we also searched for independent risk factors related to the presence of extragastroesophageal symptoms. Mild erosive esophagitis was identified as a risk factor for extragastroesophageal symptoms including foreign body sensation of throat, throat cleaning, and cough. Male gender was identified as a negative factor for cough symptom and metabolic syndrome as a negative factor for sore throat. In previous ProGERD study [6], female gender, old age, severity of erosive reflux disease, duration of GERD, and smoking were identified as risk factors for the occurrence of extraesophageal disorders.

Our study has several limitations. The true prevalence of extragastroesophageal symptoms is difficult to determine because it is difficult to evaluate whether GERD is the cause of extragastroesophageal condition or whether the two conditions coexist independently of each other [26]. Secondly, patients with milder symptoms may take medicine over the counter, making study groups to be more highly selective. Third, the lack impedance-pH monitor and symptom correlation limited our hypothesis to the current finding.

In conclusion, the frequencies of some esophageal and extraesophageal symptoms in patients with Los Angeles grade A/B erosive esophagitis were higher than those in patients with Los Angeles grade C/D erosive esophagitis and Barrett's esophagus. The causes of different symptom profiles in different categories of GERD patients merit further investigations.

### Conflict of Interests

All authors declare no commercial association, such as consultancies, stock ownership, or other equity interests or patent-licensing arrangements.

### Authors' Contribution

Sung-Shuo Kao and Wen-Chih Chen contributed equally to the work.

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## Review Article

# Current Advances in the Diagnosis and Treatment of Nonerosive Reflux Disease

Chien-Lin Chen<sup>1</sup> and Ping-I Hsu<sup>2</sup>

<sup>1</sup> Department of Medicine, Buddhist Tzu Chi General Hospital and Tzu Chi University, Hualien 970, Taiwan

<sup>2</sup> Division of Gastroenterology, Department of Internal Medicine, Kaohsiung Veterans General Hospital and National Yang-Ming University, Kaohsiung 813, Taiwan

Correspondence should be addressed to Ping-I Hsu; [williamhsup@yahoo.com.tw](mailto:williamhsup@yahoo.com.tw)

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Nonerosive reflux disease (NERD) is a distinct pattern of gastroesophageal reflux disease (GERD). It is defined as a subcategory of GERD characterized by troublesome reflux-related symptoms in the absence of esophageal mucosal erosions/breaks at conventional endoscopy. In clinical practice, patients with reflux symptoms and negative endoscopic findings are markedly heterogeneous. The potential explanations for the symptom generation in NERD include microscopic inflammation, visceral hypersensitivity (stress and sleep), and sustained esophageal contractions. The use of 24-hour esophageal impedance and pH monitoring gives further insight into reflux characteristics and symptom association relevant to NERD. The treatment choice of NERD still relies on acid-suppression therapy. Initially, patients can be treated by a proton pump inhibitor (PPI; standard dose, once daily) for 2–4 weeks. If initial treatment fails to elicit adequate symptom control, increasing the PPI dose (standard dose PPI twice daily) is recommended. In patients with poor response to appropriate PPI treatment, 24-hour esophageal impedance and pH monitoring is indicated to differentiate acid-reflux-related NERD, weakly acid-reflux-related NERD (hypersensitive esophagus), nonacid-reflux-related NERD, and functional heartburn. The response is less effective in NERD as compared with erosive esophagitis.

## 1. Definitions of Gastroesophageal Reflux Disease and Nonerosive Reflux Disease

Gastroesophageal reflux disease (GERD) has been defined in the Montreal Consensus Report as a chronic condition that develops when the reflux of gastric contents into the esophagus in significant quantities causes troublesome symptoms with or without mucosal erosions and/or relevant complications [1]. The typical symptoms of GERD are recognized as heartburn and/or acid regurgitation. GERD is a common disorder with its prevalence, as defined by at least weekly heartburn and/or acid regurgitation, estimated to range from 10 to 20% in western countries and is less than 5% in Asian countries [2]. However, it has been demonstrated that GERD is emerging as a leading digestive disorder in Asian countries [3] and has an adverse impact on health-related quality of life [4].

It is noteworthy that symptoms and esophageal lesions do not necessarily exist together. A proportion of patients with erosive esophagitis have no symptoms, whereas 50–85% of patients with typical reflux symptoms have no endoscopic evidence of erosive esophagitis [5]. The latter group of GERD patients is considered to have nonerosive reflux disease (NERD) [1].

The Vevey Consensus Group defined NERD as a subcategory of GERD characterized by troublesome reflux-related symptoms in the absence of esophageal erosions/breaks at conventional endoscopy and without recent acid-suppressive therapy [6]. There are some important developments that have emerged in the field of GERD with emphasizing the importance in managing those patients with NERD. It has been observed that most of the community-based GERD patients appear to have NERD [7]. In addition, previous studies have shown that NERD patients appear to be less

responsive to proton pump inhibitors (PPIs) as compared with patients with erosive esophagitis [8].

The axiom “no acid, no heartburn” is not theoretically proper [9, 10]. Heartburn has been demonstrated as a cortical perception of a variety of intraesophageal events [11]. Subjects with heartburn without erosive esophagitis represent a heterogeneous group of patients of whom some may not have gastroesophageal-reflux- (GER-) related disorder [12–15]. In clinical practice, patients with reflux symptoms and negative endoscopic findings can be classified as (1) acid-reflux-related NERD (increased acid reflux), (2) weakly acid-reflux-related NERD (weakly acid reflux with positive symptom association; hypersensitive esophagus), (3) nonacid-reflux-related NERD (nonacid reflux with positive symptom association), and (4) functional heartburn (no associations between symptoms and reflux) (Table 1) [13]. The Rome II committee for functional esophageal disorders defined functional heartburn as an episodic retrosternal burning in the absence of pathologic GERD, pathology-based motility disorders, or structural explanations [12]. Patients with functional heartburn should be excluded from NERD because their symptoms are not related to GER.

## 2. Natural History of NERD

Recent studies regarding natural history of NERD are limited with some shortcomings including retrospective design, irregularity in follow-up, and confounding with use of medication. Very low proportion of NERD patients (3–5%) develops erosive esophagitis with the duration up to 20 years with intermittent use of antireflux therapy [16, 17].

In a recent retrospective study on 2306 GERD patients with at least two separate upper endoscopies during a mean follow-up of 7 years, it was shown that most of the patients remained unchanged, while only 11% of patients worsened [18]. Similarly, the other study on patients with mild erosive esophagitis for a mean duration of 5.5 years suggests that, even within the different gradings of erosive esophagitis, the progression to severe disease is uncommon over time [19]. Therefore, the current notion regarding natural course of NERD indicates that the progression of NERD to severe form of GERD is uncommon, and there is no evidence to develop Barrett’s esophagus over time [20].

## 3. Prevalence of NERD

It is difficult to estimate the true prevalence of NERD, since it is hard to identify community subjects with symptoms without seeking medical attention. There are several community-based studies in Europe that found that about 70% of the patients met the diagnosis for NERD [21]. Other international studies on subjects in primary care centers showed that about 50% of their enrolled patients had normal upper endoscopy [22]. A US study on subjects who had their reflux symptoms controlled by antacids alone has shown that 53% of those subjects had no erosive esophagitis on upper endoscopy [23]. From the previous studies, the prevalence of NERD is therefore estimated to be between 50% and 70% of the GERD

population in western countries. In Asia, NERD is reported to affect different ethnic GERD populations such as 60% to 90% of the Chinese, 65% of the Indians, and 72% of the Malay [24].

## 4. Pathogenesis of NERD

Recent studies have provided greater insight into the pathophysiology and symptom generation in NERD. The major concepts in the pathophysiology we review include the pattern of mucosal response to gastric contents during reflux and on mucosal factors that may affect symptom perception.

Both esophageal dysmotility and hiatal hernia are less common in NERD than in erosive esophagitis [25]. The pathophysiology as reduced ability to clear acid from the esophagus following reflux events in patients with erosive disease is thus uncommon in NERD patients; however, the latter group is characterized by greater esophageal sensitivity in the proximal esophagus [26]. Despite no difference in gastric acid output between NERD and esophagitis [27], NERD patients have lower acid reflux when compared with patients with erosive esophagitis and Barrett’s esophagus [28]. In addition, there is considerable overlap in acid exposure times between three groups of GERD patients [29]. Proximal migration of acid and nonacidic reflux seems to play a role in the symptom generation in NERD [26]. Total acid and weakly acidic reflux are greater in erosive esophagitis and Barrett’s esophagus than in NERD [30], but NERD patients are shown to be of more homogenous distribution of acid exposure throughout the esophagus with greater proximal reflux [31]. With the advantage of impedance studies, NERD patients are shown to have greater proximal extent of reflux episodes (with and without prolonged esophageal acid exposure) than in healthy controls [32]. Further studies have shown greater proximal extent of reflux events which appears to be associated with symptom perception in GERD patients refractory to acid-suppression therapy [33]. Furthermore, some of the NERD patients are more sensitive to weakly acid reflux than those with erosive esophagitis [34], supporting the explanation for poor PPI response in NERD patients.

The potential explanations for the symptom generation in NERD include microscopic inflammation, visceral hypersensitivity (stress and sleep), and sustained esophageal contractions [35]. It has been observed that acid exposure disrupts intercellular connections in the esophageal mucosa, producing dilated intercellular spaces (DIS) and increasing esophageal permeability, allowing refluxed acid to penetrate the submucosa and reach chemosensitive nociceptors [36]. DIS has been observed in both NERD and erosive disease without a significant specificity as is also found in 30% of asymptomatic individuals [37]. DIS has been found to regress with acid suppression [38]. The development of DIS may also be potentiated by bile acids and by stress [39, 40]. Stress alone may increase esophageal permeability, provoking DIS that can be enhanced by acid exposure [40]. These observations suggest a complex relationship between stress and acid exposure in the generation of reflux symptoms.

Peripheral receptors are shown to be mediating esophageal hypersensitivity due to acid reflux including

TABLE 1: Classification of patients with reflux symptoms.

Classification	Distal esophageal acid exposure	Symptom correlation	Symptom response to PPI
Erosive esophagitis	Increased	(+)	Good
Barrett's esophagus	Increased	(+)	Good
NERD			
Acid reflux related	Increased	(+)	Good
Weakly acid related	Not increased	(+)	Moderate*
Nonacid related	Not increased	(+)	Poor*
Functional heartburn	Not increased	(-)	Poor

\*Not well investigated.

upregulation of acid sensing ion channels, increased expression of TRPV1 receptors (transient receptor potential vanilloid type 1) [41], and prostaglandin E-2 receptor (EP-1) [42]. Peripheral and central mechanisms have also been shown to influence processing of visceral sensitivity [43]. It has been demonstrated that acute laboratory stress increased sensitivity to intraesophageal acid perception in patients with GERD [44], suggesting that the increase in perceptual responses to acid was associated with greater emotional response to the stressor. Sleep deprivation has also been shown to induce acid-related esophageal hypersensitivity [45], although there is no difference in sleep disturbance between patients with erosive esophagitis and NERD [46].

## 5. Risk Factors

GERD has been demonstrated to be influenced by genetic factors in some of the patients. In a genetic study on monozygotic twins with GERD, a significant association was found between reflux symptoms and several lifestyle factors by controlling for genetic influences [47]. Obesity was independently associated with reflux symptoms in women, but was not evident in men [47]. Smoking and physical activity at work appear to be risk factors, whereas recreational physical activity is protective [47]. Independent associations have also been reported between reflux symptoms and anxiety, depression [48], and low socioeconomic status [49]. However, it is yet unclear whether there is a specific correlation between psychological comorbidity and esophageal mucosa injury [50]. There is a higher than expected prevalence of irritable bowel syndrome (IBS) in patients with GERD symptoms [51, 52]. A recent population-based study confirmed a significant overlap between reflux symptoms and IBS, with both occurring together more frequently than expected [53].

It appears that it is the NERD group that contributes most to the phenomenon as it is the predominant phenotype of patients with GERD symptoms, whereas some patients with erosive esophagitis may have no symptoms. Although an earlier work has attempted to compare clinical characteristics of NERD patients with those of erosive diseases patients in the same population, the potentially confounding contribution from functional heartburn has not been fully controlled [54]. Previous studies have shown that NERD patients are more likely to be female and leaner as compared with those with

TABLE 2: Clinical and physiological characteristics between patients with NERD and erosive esophagitis.

Characteristics	NERD	Erosive esophagitis
Gender	Female	No difference
Age (yr)	40–50	50–60
Smoking (%)	15–23	10–23
Alcohol (%)	8–59	6–64
Symptom duration (yr)	1–5	1–5
Hiatal hernia (%)	20–29	39–56
<i>Helicobacter pylori</i> (+) (%)	34–41	20–26
Resting LES pressure	Normal	Normal to low
Abnormal esophageal motility	Mild	Moderate to severe
Esophageal acid clearance	Normal	Abnormal
Distal esophageal pH (<4) (% of time)	Slightly increased	Moderately increased

NERD: nonerosive reflux disease; mild: ineffective esophageal motility alone; moderate to severe: ineffective esophageal motility and impaired bolus clearance.

erosive esophagitis [22]. NERD patients are also less likely to have a hiatus hernia and more likely to have *Helicobacter pylori* [22]. Further studies in patients with NERD and erosive esophagitis indicate that both groups of the patients appear to have distinct differences regarding clinical and physiological characteristics (Table 2) [22, 25, 55].

Recent data from Taiwan showed higher neuroticism scores in patients with reflux symptoms (with and without esophagitis) than in patients with asymptomatic esophagitis [50]. In a further study from Hong Kong, which excluded functional heartburn, IBS was independently associated with NERD instead of erosive esophagitis [25]. In addition, NERD patients were found to have increased tendency to have functional dyspepsia, psychological disorders, and positive acid perfusion test [25]. However, clinical studies show equal influence between NERD and erosive esophagitis regarding heartburn intensity [56], quality of life [57], and sleep dysfunction [46].

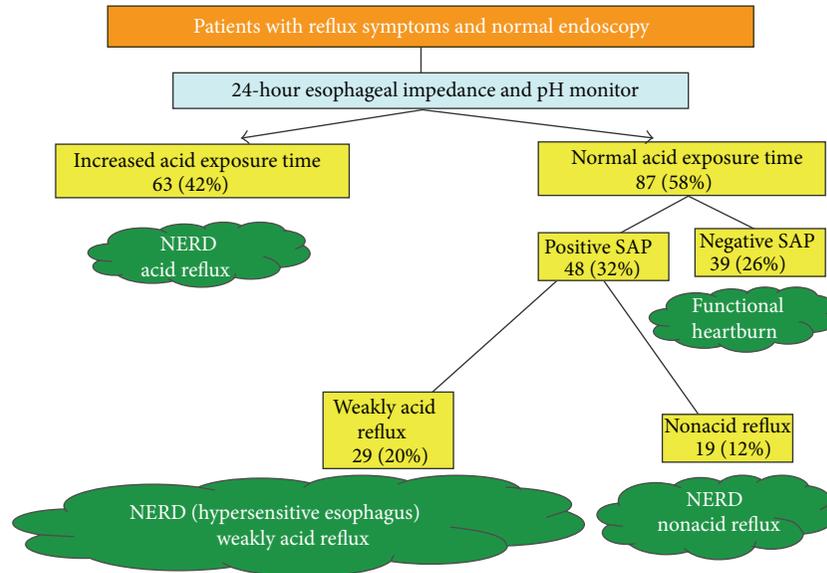


FIGURE 1: Classification of patients with reflux symptoms and normal endoscopy (SAP: symptom association probability).

## 6. Diagnosis of True NERD and Functional Heartburn

**6.1. Endoscopic Image.** Currently, NERD is differentiated from erosive esophagitis by white light endoscopy, and NERD is further differentiated from functional heartburn by using pH monitoring ( $\pm$ impedance) with symptom reflux association. Recent technological advances may improve diagnostic sensitivity regarding upper endoscopy. Due to a significant overlap in the amount of reflux episodes between patients with NERD and erosive esophagitis [30], it is suggested that mucosal changes in NERD patients may be too subtle to be detected by conventional endoscopy. A recent study has confirmed the clinical utility of magnification endoscopy with narrow band imaging (NBI) which provides detailed findings in reflux diseases which are not visible by conventional endoscopy [58]. This study has shown several subtle changes in the esophageal mucosa which were identified to be highly associated with reflux disease. NERD patients appear to have intrapapillary capillary loops and microerosions identified on NBI than controls. The notation is also evident in subgroup analysis when NERD patients and esophagitis patients were compared with controls. However, despite excellent interobserver agreement for NBI findings, the drawback of NBI alone is present as modest intraobserver agreement has been demonstrated [58]. Further studies of NBI suggest that combined NBI with conventional findings gives the resolution for improving diagnostic accuracy for NERD by upper endoscopy [59].

**6.2. 24-Hour Impedance pH Monitoring.** 24-hour esophageal pH monitoring has been criticized for having limited sensitivity in diagnosing GERD; however, this technique is still essential for the diagnosis of NERD. The limitation of conventional pH monitoring has been overcome by combining

pH with impedance monitoring [13, 60]. 24-hour impedance pH monitoring enables detection of acidic, weakly acidic, and nonacidic reflux and correlation with symptoms. This technique is able to identify three subsets of NERD (i.e., patients with an excess of acid, with a hypersensitive esophagus [to weakly acidic reflux], or with nonacid-reflux-related symptom) and patients with functional heartburn. Savarino et al. investigated the data of combined impedance pH monitoring in 150 patients with reflux symptoms and negative endoscopy under off-PPI condition (Figure 1). It was concluded that adding impedance to pH monitoring improved the diagnostic sensitivity mainly by identifying a positive symptom association probability with weakly acid or nonacid reflux in patients off PPI therapy [13]. By using this advanced technique in a group of patients with reflux symptoms not taking PPI, it was observed that the value of adding impedance measurement to standard pH monitoring could increase the observed positive symptom-reflux event association that might improve the diagnostic sensitivity of NERD [61]. From the findings previous, although combined impedance and pH measurement is necessary to reliably distinguish NERD patients from patients with functional heartburn, the test is not commonly used in general practice, and the response to PPI is more realizable than to identify those with functional heartburn [62]. Furthermore, NERD with weakly acid reflux is relatively uncommon without the condition during acid-suppression treatment.

## 7. Treatment of NERD

**7.1. PPIs.** PPIs are the most recommended and effective agents employed in the treatment of GERD. The advantage of PPIs relieving reflux symptoms is also found in NERD patients. PPIs are more effective than other acid-suppressing agents such as histamine-2 receptor antagonists (H2RAs).

It has been demonstrated in NERD patients that the relative risk for PPIs versus H2RAs was 0.74 (95% CI: 0.53–1.03) for controlling heartburn [63].

Initially, patients can be treated by a proton pump inhibitor (PPI; standard dose, once daily) for 2–4 weeks. If initial treatment fails to elicit adequate symptom control, increasing the PPI dose (standard dose PPI twice daily) is recommended. In patients with poor response to appropriate PPI treatment, esophageal pH ( $\pm$ impedance) monitoring is indicated to differentiate pathological acid reflux, acid-sensitive (hypersensitive) esophagus, and functional heartburn. The beneficial effects of PPIs in achieving symptom relief in NERD have been well documented in several studies. The rates of the relief of symptoms are shown to be 40–60% for omeprazole and rabeprazole 20 mg/day and about 30% for omeprazole 10 mg/day for 4 weeks [7, 64, 65]. By using the wireless Bravo pH monitoring, normalization of esophageal acid exposure is found in NERD patients within 48 hours after starting PPIs [66].

NERD patients have been shown to be less responsive to PPIs as compared with patients with erosive esophagitis by approximately 20–30% after 4 weeks of the treatment [8]. The overall PPI symptomatic response rate was 36.7% (95% CI: 34.1–39.3) in NERD and 55.5% (95% CI: 51.5–59.5) in erosive esophagitis, whereas the rate of therapeutic gain was 27.5% in NERD and 48.9% in erosive esophagitis [8]. In NERD patients, the response rate appears to positively correlate with the extent of distal esophageal acid exposure with the higher symptom resolution in patients with greater acid exposure [7]. Furthermore, patients with NERD demonstrate similar symptomatic response to half and full standard dose of PPI as a prior study has shown a similar median time to first symptom relief (2 days) and to sustained symptom relief (10–13 days) for pantoprazole (20 mg/day) and esomeprazole (20 mg/day) [67]. In a subsequent study, administration of a lower dose of rabeprazole (5 mg/day) is not superior to half dose rabeprazole (10 mg/day) for heartburn relief [68].

Studies have demonstrated that on-demand or intermittent PPI therapy is also an effective strategy in NERD treatment [69]. Due to the fact that most of the NERD is less likely to be progressive [20, 70], treatment for those patients can be tailored by the presence of their symptoms. Therefore, on-demand or intermittent therapy is widely used as alternative PPI treatment for NERD patients [71, 72], which also has the advantage of convenience, stable acid control, cost effectiveness, and reducing the chance of acid rebound.

Dexlansoprazole MR is an R-enantiomer of lansoprazole with dual delayed-release benefit in prolonging plasma concentration and pharmacodynamic effects better than those of single-release PPIs with its administration allowed at any time of the day without regard to meals. In patients with NERD, dexlansoprazole MR 30 mg daily has been shown to be more efficacious than placebo in controlling heartburn [73].

**7.2. Novel Therapeutic Modalities.** There are novel therapeutic modalities developed specifically for NERD patients. The targets for novel therapy are thought to be improving the

competence of LES function such as new GABA-B agonists, better acid-suppression therapy, normalizing esophageal sensitivity, and augmenting esophageal motility. In patients with failure to respond to PPI treatment, it has been suggested that pain modulators like tricyclics and selective serotonin reuptake inhibitors are an alternative treatment option for controlling refractory symptoms such as heartburn and chest pain [74, 75]. However, there is no sufficient evidence to support their efficacy in PPI-failure patients. In patients with PPI failure, the use of pain modulators alone or combined with PPIs can be a treatment strategy, but further studies need to confirm such approach in PPI-failure patients.

The role of antireflux surgery NERD has not been well established. In general, NERD patients are less responsive to antireflux surgery [76]. In one earlier study comparing the clinical outcome of antireflux surgery between patients with erosive esophagitis and NERD, it was demonstrated that 91% versus 56% reported heartburn resolution, 24% versus 50% reported dysphagia after surgery, and 94% versus 79% were satisfied with surgery, respectively [76].

## 8. Conclusions

The definition of GERD is well established and simply understood, whereas the NERD has been intangibly defined with more conditions needed, largely because of the increased recognition of functional heartburn due to the evolution of the Rome criteria for functional gastrointestinal disorders. NERD is generally accepted as an entity within the broader definition of GERD by excluding functional heartburn. NERD has been increasingly recognized as the most common cause of reflux symptoms in community population with impact on quality of life. Mechanisms of the symptom generation in NERD remain complex, and stress may play a role in the symptom generation. Treatment with PPIs remains the choice of the therapy in NERD patients, but may be less effective when compared with those with erosive esophagitis. The role of anti-reflux surgery in NERD remains to be further investigated and defined. PPIs therapy with intermittent or on-demand fashion can be an alternative treatment strategy in most of the NERD patients due to the relatively low risk for the progression to erosive esophagitis or Barrett's esophagus.

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## Review Article

# Antireflux Endoluminal Therapies: Past and Present

**Kuo Chao Yew<sup>1</sup> and Seng-Kee Chuah<sup>2</sup>**

<sup>1</sup> *Department of Gastroenterology and Hepatology, Tan Tock Seng Hospital, 11 Jalan Tan Tock Seng, Singapore 308433*

<sup>2</sup> *Division of Hepatogastroenterology, Department of Internal Medicine, Kaohsiung Chang Gung Memorial Hospital, Chang Gung University College of Medicine, 123 Ta-Pei Road, Niao-Sung Hsiang, Kaohsiung 833, Taiwan*

Correspondence should be addressed to Seng-Kee Chuah; [chuahsk@seed.net.tw](mailto:chuahsk@seed.net.tw)

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The basic principle of antireflux procedures employing endoscopic intervention aims to create a mechanical barrier to prevent primary pathophysiology in gastroesophageal reflux disease (GERD). We review, highlight, and discuss the past and present status of endoluminal therapy. Currently, there are 3 commonly employed anti-reflux endoluminal procedures: fundoplication or suturing techniques (EndoCinch, NDO, and EsophyX), intramural injection or implant techniques (enhancing lower esophageal sphincter (LES) volume and/or strengthening compliance of the LES-Enteryx and Gatekeeper), and radiofrequency ablation of LES and cardia. EndoCinch plication requires further study and modification of technique before it can be recommended because of durability issues. Esophynx, the transoral incisionless fundoplication, may reduce hiatal hernias and increase LES length. Preliminary studies have shown promising reduction in symptoms and medication use but evidence concerning safety and long-term durability is still pending. The safety issue with injection technique is the main concern as evident from the incidences of implant withdrawals after reported major adverse events. Future research with cautious monitoring is required before any new implant material can be recommended for commercial application. Radiofrequency ablation therapy is regaining popularity in treating refractory symptoms despite PPI use due to improved efficacy, durability, and safety after years of refinement of protocol.

## 1. Introduction

Gastroesophageal reflux disease (GERD) is a disease spectrum caused by regurgitation of stomach contents causing troublesome esophageal or extraesophageal symptoms as defined by Montreal definitions [1]. Either mild heartburn and/or regurgitation for at least 2 days per week or moderate to severe symptoms for at least one day per week qualifies as significant symptom-based diagnosis [2]. Phenotypical classifications of GERD are nonerosive reflux disease (NERD), erosive esophagitis (EE), and Barrett's esophagus (BE). Population-based study reported 15%–20% of the Western population experience reflux on a weekly basis which can lead to impoverishment of a country's economy and quality of life [3]. Dent et al. reported the prevalence of GERD in Sweden (15.5%), Italy (11.8%), China, Japan, Korea (3.4%–8.5%), and Taiwan (9%–24.6%), respectively [4]. Subanalysis shows that EE and hiatus hernia are more common in Europe than in Asia with the exception of Taiwan which reported

similar EE prevalence as Europe. Over years, the prevalence of GERD is increasing by approximately 5% annually amongst the American population and other countries in the West such as Western Europe and Scandinavia [5]. Furthermore, the prevalence of GERD is also increasing in Asian countries [6]. Taiwan, with a population consisting mainly of Chinese ancestry, has one of the most published data on GERD. Yeh et al. reported 14.5% of prevalence in 1991 [7] only to be superseded by a prevalence of approximately 25%–26% from 2007 to 2011 [8, 9]. The social impact of GERD includes lost work days and increased public health cost. Medically, there is a risk of developing esophageal adenocarcinoma (EAC). Barrett's esophagus will develop in an incidence rate of 0.5% per year and Barrett's esophagus is a risk for esophageal adenocarcinoma (EAC) or of a 400-fold increased risk of EAC [10]. GERD increases the risk of EAC by 8.6-fold [11].

GERD and its associated clinical manifestations present a diagnostic challenge. A third of patients with GERD present with atypical symptoms or in fact may be asymptomatic.

Wong et al. reported extraesophageal presentation or atypical complaints such as asthma (4.8%), chronic cough (13%), and laryngeal disorder (10%) [12]. Some authors have suggested a trial of proton pump inhibitors (PPI) with a temporal improvement in symptoms as an indirect diagnostic method but the risk is that BE, RE, and even EAC may be missed [13].

PPI have been the most effective treatment for GERD but discontinuation of medical therapy is likely to lead to clinical relapse. Long-term PPI users and patients who are noncompliant with daily PPI dosage may run into problems such as refractory GERD, NERD, EE, and BE. Side effects of PPI use that are gaining more attention amongst physicians include an increased incidence of hip fracture in postmenopausal women, pneumonia, enteric infections, and drug-drug interactions with clopidogrel. With long-term PPI use, there is also the issue of compliance and financial health costs. Therefore, some patients may be more suited to other treatment options such as surgery or endoscopic intervention. Antireflux procedures either via surgery or endoscopic intervention aim to create a mechanical barrier to prevent primary pathophysiology in GERD. In this paper, we review, highlight, and discuss the past and present status of the endoluminal therapies.

## 2. GERD Pathophysiology

The pathophysiological mechanisms of GERD are transient LES relaxation (TLESR), low LES pressure, and GEJ anatomic distortions such as hiatal hernia [14]. Dysfunctional esophageal motility, impaired barrier function of LES, and gastric emptying in relation to meal intake may all lead to gastric content reflux. LES relaxation can be triggered by 3 main motor events: deglutitive inhibition during the swallowing process, secondary peristalsis from esophageal distention, and cardiac distention mediated relaxation of LES. The third mechanism is transient TLESR with the sensory trigger point located distal to LES [15]. It is the total relaxation duration and not the frequency that contributes to this pathophysiology. Classical description involves relaxation of LES, esophageal shortening, and inhibition of crural diaphragm. A disruption in the musculature plane such as hiatal hernia will blunt the angle of His and impair the flap valve mechanism. The GERD condition is mostly accompanied by the formation of a gastric air pocket which can stimulate the acid sensing ion channel primarily located around the cardia leading to TLESR [15]. Often it is bile acid that causes more mucosal damage than gastric secretion.

## 3. Rationale of Antireflux Endoluminal Therapy

PPI therapy to decrease acid output cannot provide a physical barrier or restore the LES function [16]. Relapses in esophageal and extraesophageal disease are also indications for more definitive treatment. Chen et al. reported that bile acid disrupts squamous epithelial barrier function by modulating TJ proteins, demonstrating the importance of the integrity of an antireflux barrier in addition to established acid suppressive therapy [17]. Some patients may not

tolerate long-term medical therapy or be a candidate for surgery. Under such circumstances, endoluminal antireflux interventions may be a viable option. Antireflux endoscopic intervention aims to create a mechanical barrier to prevent the regurgitation of gastric contents into the esophagus. An appropriate high pressure zone at LES needs to be produced to aid the closure of diaphragmatic crural fibers and the His angle of the gastroesophageal junction. An anatomic-physiological flap valve at gastroesophageal junction can be created by antireflux barrier reconstruction of collar sling musculature at the cardia [18]. The antireflux barrier reconstruction procedure aims to reconstruct the acute angle of His by enveloping the distal esophagus to the proximal stomach mimicking an intragastric valve that will prevent regurgitation of food in the presence of intragastric and intra-abdominal pressure [19].

Hill and Kozarek demonstrated that the LES pressure gradient can be increased by suturing a flap valve (valvuloplasty) which can then be further enhanced with the posterior attachment of gastroesophageal junction [20]. With hiatus hernia, suturing the GEJ to a fixation point intra-abdominally at the preaortic fascia will have a similar effect. The presence of an intragastric mucosal ridge is far more important in determining antireflux effect rather than an increased LES pressure gradient. The valvular appearance is a good predictor of the reflux status. As there are limitations in endoscopic manipulation of the esophagus, careful patient selection with little or no hiatal hernia is important to determine the success of this approach [18]. In general, a large hiatal hernia (especially paraesophageal) should be referred for laparoscopic or open surgery. Other contraindications for antireflux endoluminal therapy include patients with refractory symptoms despite maximum therapy, esophageal strictures, dysmotility and Barrett's esophagus, severe liver disease, portal hypertension, varices, and coagulopathy [18].

Indications for antireflux endoluminal therapy are refractory GERD, PPI intolerance, a desire to stop drug therapy with concerns of long-term side effects, concerns about laparoscopic antireflux surgery side effects such as dysphagia, gas bloat, and finally symptomatic GERD after fundoplication.

## 4. Antireflux Endoluminal Therapy

Development of the antireflux endoluminal therapy was an attempt at correcting GERD's pathophysiology by increasing the LES pressure, reducing the frequency of TLESR, antireflux barrier construction, attenuation of esophageal sensation against refluxate, and anatomical reconstruction improving the angle of His or cardia for flap valve creation [21]. The available antireflux endoluminal therapies can be divided into fundoplication or suturing techniques (EndoCinch, NDO, and EsophyX), intramural injection or implants techniques (Enteryx, Gatekeeper), and radiofrequency ablation of LES and cardia (Stretta system) (Table 1). Procedures such as Endocinch and Stretta RFA are safe outpatient procedures [21, 22].

TABLE 1: Anti-reflux endoluminal therapies.

(1) Endoscopic fundoplication or suturing techniques	
EndoCinch	A landmark procedure approved by FDA in 2000 till today but the durability is poor even after enhanced modification
NDO PLICATOR	A full-thickness suturing transmural plicator to address the weakness of EndoCinch with successful creation of a more effective mechanical barrier but had been retrieved from market due to the company's poor financial performance
Esophyx	This transoral incisionless fundoplication (TIF) has the advantage that it can reduce hiatal hernia up to 2 cm, which is often not possible with other anti-reflux endoluminal therapies. Serious complications such as esophageal perforation and postoperative bleeding were reported
(2) Injection/implantation techniques	
Gatekeeper reflux repair system and Enteryx	(1) Creation of an anti-reflux barrier by a bulking effect at LES which included injection of bovine dermal collagen, Teflon, polymethylmethacrylate microspheres (Plexiglas), and polytetrafluoroethylene (Polytef) with no remarkable benefits (2) They were removed from the market due to unsatisfactory benefit from symptoms control or objective measurement of anti-reflux properties and various degrees of complications
(3) Radiofrequency ablation	
Stretta system	(1) It was first introduced in 2000 and utilizes an inflatable balloon-mounted device that introduces 4 electrodes at the LES with RFA energy delivered under controlled temperature to produce a coagulation inflammation, necrosis, and fibrosis. The technology has refined the recommended dosage to avoid serious complications (2) It had gained popularity in recent years and is being used as a first line treatment option for refractory GERD before surgical salvage

FDA: food and drug administration; TIF: transoral incisionless fundoplication; LES: lower esophageal sphincter; RFA: radiofrequency ablation; GERD: gastroesophageal reflux disease.

**4.1. Endoscopic Fundoplication or Suturing Techniques.** Endoscopic fundoplication can be accomplished using the EndoCinch (C.R. Bard Inc., Murray Hill, NJ, USA), EsophyX (EndoGastric Solutions, Redwood City, CA, USA), and SRS endoscopic stapling (Medigus Ltd., Tel Aviv, Israel) systems [21]. The procedure may be used to improve LES tone, remodel GEJ, and alter lower esophageal length. This would reduce esophageal sensitivity and improve gastroesophageal flap valve grading.

**4.1.1. EndoCinch.** This landmark procedure was described by Swain and Mills in 1986 and subsequently approved in April 2000 by FDA. Till today it remains a popular option with well-studied research and is often compared to surgical fundoplication [23]. However, intermediate to long-term performance of Endocinch is considered poor with endoscopic ultrasound demonstrating loosening of sutures from lack of full thickness fundoplication and poor mucosa apposition with sutures even after enhanced modification [24, 25]. There is no marked improvement in its durability in the sham-controlled study [26]. There was no obvious reversal of esophagitis and no improvement in pH evaluation [26]. Complications such as mucosal tear and microperforation have been reported but the number was small. Moreover, the efficacy of EndoCinch was shown to be inferior to surgical fundoplication [27].

**4.1.2. NDO PLICATOR.** In 2003, NDO Surgical Company, USA, designed a full-thickness suturing transmural plicator to address the weakness of EndoCinch. The pilot study conducted by Chuttani et al. proved the safety of the procedure in humans [28]. The device created a valve resembling partial fundoplication. Rothstein et al. reported

an extended improvement in QoL and reduction in PPI usage at 5 years when compared to the sham study [29]. The time reduction for pH < 4 after full-thickness plication (FTP) suggested the successful creation of a more effective mechanical barrier. Jeansonne IV et al. reported a superiority of NDO FTP against radio frequency ablation (RFA) in an obese cohort and also in patients with major complaints of regurgitation [30]. Larger hiatus hernia (especially >2 cm) and loose cardia diameter resulted in failure of procedure [13]. Technique modification such as application of 2 plications at slight diagonal vector was superior to conventional methods [30]. However, this procedure had similar side effects to fundoplication such as dysphagia, dysphonia, and cough [23]. The device was retrieved from market in June 2008 due to the company's poor financial performance. However, there are other competitive devices such as Antireflux Device (ARD; Syntheon, Miami, FL, USA), the His-Wiz (Olympus, Center Valley, PA, USA), and the EsophyX (EndoGastric Solutions, Redmond, WA, USA) [25].

**4.1.3. EsophyX.** EsophynX, the transoral incisionless fundoplication (TIF), was evaluated in 2006. It utilizes suction and transmural fasteners for the application of an uninterrupted suture line at the base of LES and opposing gastroesophageal junction to the fundus, thus creating a neoesophageal valve of 2–6 cm (average 4 cm) and 230° in circumference (range 160–300°) and restoring the angle of His, closely resembling those of Nissen fundoplication products. There is no repeated device intubation requirement [23]. More importantly it can be used to reduce hiatal hernia up to 2 cm, which is often not possible with other antireflux endoluminal therapies [7]. Cadière et al. reported total hiatal hernia reduction and

beneficial increment of LES length after procedure [31]. However, serious complications such as esophageal perforation and postoperative bleeding were reported [21].

**4.2. Injection/Implantation Techniques.** There were numerous attempts to create an antireflux barrier by a bulking effect at LES which included injection of bovine dermal collagen, Teflon, polymethylmethacrylate microspheres (Plexiglas), and polytetrafluoroethylene (Polytef) with no remarkable benefits [32]. Devices such as Gatekeeper Reflux Repair System (Medtronic Inc., Minneapolis, MN, USA) and Enteryx (Boston Scientific Corporate, Natick, MA, USA) were removed from the market because of unsatisfactory benefit from symptoms control or objective measurement of antireflux properties and various degrees of complications. Cicala et al. reported pharyngeal perforation in a patient resulting in mediastinitis or surrounding organ inflammation after error in injection techniques at early postmarketing phase in 2005 [33].

To date, the safety issue of injection techniques is still in the main concern [34]. Therefore, further research and observation are required before it can be recommended for commercial application. The major obstacle to injection techniques is that the implant material must meet the criteria of producing minimal inflammation to surrounding organs.

**4.3. Radiofrequency Ablation.** Radiofrequency Ablation (RFA), Stretta system (Curon Medical, Fremont, CA, USA), was first introduced in 2000 [35]. It utilizes an inflatable balloon-mounted device that introduces 4 electrodes at the LES with RFA energy delivered under controlled temperature to produce a coagulation inflammation, necrosis, and fibrosis. The RFA energy is emitted circumferentially, extending from 2 cm above to 1.5 cm below the gastroesophageal junction and an additional six sets below the cardia [35–37]. The RFA energy can induce neurolysis of LES vagal nerve which results in reduced frequency of TLESR, improvement of gastric emptying, and also increasing the gastric yield pressure level needed to cause reflux episodes [38, 39]. It can also reduce esophageal sensitivity, inducing remodeling of the compliance of gastroesophageal junction and hence increasing the LES resistance [40]. Abdel Aziz et al. reported that the total esophageal acid exposure was reduced after-procedure and sustained at 12th month of evaluation [37].

The Stretta system improves GERD symptoms and reflux control, alleviates heartburn, and reduces PPI requirement in nearly two-thirds of patients [41]. Reymunde and Santiago reported a 4-year followup with sustained improvements in symptoms, quality of life, and drug use after the procedure [42]. The efficacy was again demonstrated by Dughera et al. which showed that 72.3% of patients remained PPI free at month 48 [39]. Most of the antireflux endoluminal procedures do not alter the esophageal acid exposure and fail to demonstrate reversibility of the esophagitis which is the early manifestation of BA and EAC development. The Stretta is able to improve the severity of esophagitis [43].

Over the years, the Stretta technology has refined the recommended dosage to avoid serious complications. The early

Stretta technique made 112 lesions at gastroesophageal junction resulting in some cases of esophageal perforation. A technical modification by Aziz group with the total number of lesions made reduced to 56 per session with a double-dose RFA energy delivered 4 months apart has been proven to be less harmful than a single vigorous dose with double the efficacy [37]. The adverse events of the Stretta procedure are mostly mild and transient such as transient chest discomfort (26.7%), fever (7.1%), and dysphagia (7.1%) [41]. The paradoxical adverse event of delayed gastric emptying is variable which could be due to the effect of double-dose RFA energy causing vagal nerve damage at gastric fundus which results in gastroparesis. Other significant complications reported by United States Food and Drug Administration are bleeding, mucosal injuries, aspiration, and effusion [44].

As this procedure can be done easily in an outpatient setting, the Stretta system had gained popularity in recent years and is being used as a first line treatment option for refractory GERD before surgical salvage [8]. Patients with sliding hernia more than 2 cm, severe reflux esophagitis (Los Angeles classification grade C/D), erosive esophagitis despite optimal PPI therapy, and primary extraesophageal conditions such as asthma should be excluded from this procedure [39].

## 5. Conclusions

Gastroesophageal reflux disease (GERD) is an increasing prevalent clinical condition affecting a significant portion of the population. This increase in incidence may well be associated with the awareness amongst medical practitioners and more efficient diagnostic techniques as well as other lifestyle factors. However, with the advent of minimally invasive procedures such as the various endoluminal techniques, there is now an increased array of management options available in addition to the traditional drug therapy and surgery. Current endoscopic intraluminal procedures gaining popularity include endoscopic fundoplication and radiofrequency ablation. These and any future minimally invasive endoscopic procedures certainly would be welcomed in addition to the management of GERD and would hopefully help to further alleviate the suffering of many GERD patients.

## Conflict of Interests

All authors declare no commercial association, such as consultancies, stock ownership, or other equity interests or patent-licensing arrangements.

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## Review Article

# Current Pharmacological Management of Gastroesophageal Reflux Disease

**Yao-Kuang Wang,<sup>1</sup> Wen-Hung Hsu,<sup>1,2</sup> Sophie S. W. Wang,<sup>1,3</sup>  
Chien-Yu Lu,<sup>1,4</sup> Fu-Chen Kuo,<sup>5</sup> Yu-Chung Su,<sup>4,6</sup> Sheau-Fang Yang,<sup>7</sup>  
Chiao-Yun Chen,<sup>3,8</sup> Deng-Chyang Wu,<sup>1,2,3,4</sup> and Chao-Hung Kuo<sup>1,3,4</sup>**

<sup>1</sup> Division of Gastroenterology, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan

<sup>2</sup> Division of Internal Medicine, Kaohsiung Municipal Hsiao-Kang Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan

<sup>3</sup> Cancer Center, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan

<sup>4</sup> Department of Medicine, Faculty of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan

<sup>5</sup> Department of Health Management, I-Shou University, E-Da Hospital, Kaohsiung, Taiwan

<sup>6</sup> Department of Internal Medicine, Kaohsiung Municipal Ta-Tung Hospital, Kaohsiung, Taiwan

<sup>7</sup> Department of Pathology, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan

<sup>8</sup> Department of Medical Imaging, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan

Correspondence should be addressed to Chao-Hung Kuo; [kjh88kmu@gmail.com](mailto:kjh88kmu@gmail.com)

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Gastroesophageal reflux disease (GERD), a common disorder with troublesome symptoms caused by reflux of gastric contents into the esophagus, has adverse impact on quality of life. A variety of medications have been used in GERD treatment, and acid suppression therapy is the mainstay of treatment for GERD. Although proton pump inhibitor is the most potent acid suppressant and provides good efficacy in esophagitis healing and symptom relief, about one-third of patients with GERD still have persistent symptoms with poor response to standard dose PPI. Antacids, alginate, histamine type-2 receptor antagonists, and prokinetic agents are usually used as add-on therapy to PPI in clinical practice. Development of novel therapeutic agents has focused on the underlying mechanisms of GERD, such as transient lower esophageal sphincter relaxation, motility disorder, mucosal protection, and esophageal hypersensitivity. Newer formulations of PPI with faster and longer duration of action and potassium-competitive acid blocker, a newer acid suppressant, have also been investigated in clinical trials. In this review, we summarize the current and developing therapeutic agents for GERD treatment.

## 1. Introduction

Gastroesophageal reflux disease (GERD) is a common gastrointestinal disorder in the general population, and its prevalence is increasing worldwide [1]. According to the Montreal definition, GERD is diagnosed when the reflux of stomach contents causes troublesome symptoms and/or complications [2], and it is the most common outpatient gastrointestinal disease diagnosed in USA [3]. Reflux from stomach causes symptoms like heartburn and regurgitation, which are the cardinal symptoms of GERD, and other symptoms, such as chest pain, asthma, hoarseness, and sleep disturbance,

are also considered as atypical or extraesophageal symptoms of GERD [4]. Troublesome symptoms of GERD have adverse impact on health-related quality of life (HRQL) [5], and patients with more frequent or more severe symptoms have lower HRQL, work productivity, and sleep quality [5, 6]. Chronic reflux is also an important risk factor of esophageal adenocarcinoma [7].

There are many factors contributing to GERD, including transient lower esophageal sphincter relaxation (TLESR), reduced LES pressure, impaired esophageal mucosal defense, poor esophageal clearance, visceral hypersensitivity, hiatal hernia, and delayed gastric emptying, and TLESRs is the

predominant mechanism of reflux formation [8]. Obesity is an independent risk factor for development of GERD and is also associated with its complications, including erosive esophagitis, Barrett's esophagus, and esophageal adenocarcinoma [9, 10]. Acid pocket is a short zone of unbuffered highly acidic gastric juice after meal. Discovery of acid pocket has been helpful in understanding postprandial acid reflux and has an influence on management strategies [11, 12]. Both erosive esophagitis and nonerosive reflux disease (NERD) are included in GERD, and the difference between them is whether mucosal damage is detected by endoscopy or not. Patients with NERD have increased sensitivity to weakly acidic or nonacid reflux and abnormal peripheral and central sensitizations resulting in symptoms in these patients [13].

Acid suppression is the mainstay of therapy for GERD and proton pump inhibitors (PPIs) are the most potent drug in this regard. Although the use of PPIs is the treatment of choice for GERD, still approximately one-third of patients with GERD fail to respond symptomatically to a standard dose PPI, either partially or completely [14, 15]. Refractory GERD, defined as reflux symptoms either completely or incompletely responsive to PPI therapy, has become an important issue in clinical practice. Treatment options, such as histamine type-2 receptor antagonist (H2RA), TLESR reducers, prokinetic agents, and alginates, could be considered as an add-on to PPI therapy for symptomatic patients after taking PPI. Newer drug and other therapeutic strategies targeting mechanism of GERD, other than acid suppression, are also being developed for patients with incomplete response to PPI. In this review, we summarize the current and developing therapeutic options for GERD treatment:

- Antacids
- Alginate
- Sucralfate
- Acid suppressants
  - Histamine type-2 receptor antagonist
  - Proton pump inhibitor
  - Potassium-competitive acid blocker
- TLESR reducers
  - GABA<sub>B</sub> receptor agonist
  - mGluR5 antagonist
- Prokinetic agents
  - Metoclopramide
  - Domperidone
  - Tegaserod
  - Mosapride
  - Itopride
  - Rikkunshito
- Pain modulators
  - Tricyclic antidepressants
  - Trazodone
  - Selective serotonin reuptake inhibitors
  - Serotonin-norepinephrine reuptake inhibitor
  - Theophylline.

## 2. Therapy Focused on Antacids and Alginate

**2.1. Antacids.** Before H2RA development, antacids were widely used as initial treatment for patient with reflux symptoms. Antacids are compounds containing different combinations, such as calcium carbonate, sodium bicarbonate, aluminum, and magnesium hydroxide. They provide rapid but short-term symptom relief by buffering gastric acid. Antacids are a convenient over-the-counter treatment for GERD, but only one-quarter of patients have symptom relief after antacid use. Nevertheless, these drugs have no efficacy in healing erosive esophagitis [16].

**2.2. Alginate.** Alginate is anionic polysaccharide occurring naturally in brown algae and has a unique property different from traditional antacids. Alginate and bicarbonate, usually contained in alginate-based formulations, interact with gastric acid to form a foamy gel, and this foamy gel, like a raft floating on the surface of gastric contents, creates a relative pH-neutral barrier [17]. Alginate-antacid formulations can reduce postprandial symptoms by neutralizing the acidity of gastric contents and, more importantly, by forming a gel-like barrier to displace the "acid pocket" from the esophago-gastric junction and protect the esophageal mucosa [18]. Like antacids, alginate-based formulations demonstrate an immediate onset of effect within 1 hour of administration, faster than PPI and H2RA [19]. Furthermore, alginate-based formulations have longer duration [17] and higher efficacy than traditional antacids in relieving reflux symptoms, even in NERD patients [20]. The mechanism of symptom relief in NERD patients treated with alginate is possibly related to protection of esophageal mucosal integrity [21]. The other potential role of alginate in GERD patients is reducing the damaging of nonacid reflux, like pepsin and bile acids [22]. A randomized double-blind double-dummy trial in moderate GERD patients showed that an alginate-based formulation, Gaviscon (4 × 10 mL/day), was noninferior to omeprazole (20 mg/day) in achieving a 24 h heartburn-free period [23]. Although alginate has less benefit in healing erosive esophagitis [24], it could be considered as an alternative or add-on therapy for symptom relief in GERD patients refractory to PPI [25].

## 3. Therapy Focused on Mucosal Protection

**3.1. Sucralfate.** Sucralfate, a complex salt of sucrose sulfate and aluminum hydroxide, contributes to mucosal protection by several different actions. It provides a physical barrier to block diffusion of acid, pepsin, and bile acids across esophageal mucosa and attenuate the erosive injury of acid and alkali. The potential benefits of sucralfate include mucosa repair and ulcer healing [26]. Sucralfate shows its efficacy in improving reflux symptoms in patients with reflux esophagitis and NERD patients [27, 28]. Like antacids and alginate, sucralfate has a limited role in healing of erosive esophagitis and is usually considered as add-on therapy for GERD treatment. For its low maternal adverse events and no teratogenicity, sucralfate is a safe drug for pregnant woman with reflux symptoms [29].

## 4. Therapy Focused on Acid Suppression

**4.1. Histamine Type-2 Receptor Antagonist (H2RA).** Before development of PPIs, H2RAs were the first acid-suppressive agents and have better efficacy than antacids in healing of erosive esophagitis and alleviating reflux symptoms. H2RA reduces gastric acid output as well as gastric acid volume by competitive inhibition of histamine at H2 receptors and reducing pepsin secretion. However, patients with severe erosive esophagitis have poorer therapeutic response to H2RA, and most patients with GERD have only improved, but not eliminated, reflux symptoms after H2RA use. H2RAs also have their limitations in treating erosive esophagitis, such as their relatively short duration of action (compared with PPIs), development of tolerance, and incomplete inhibition of acid secretion in response to a meal [30]. In meta-analysis, H2RAs are less effective than PPIs in healing of erosive esophagitis and relieving heartburn [31, 32].

Although H2RAs are not as effective as PPI in acid suppression, the potential effect of H2RAs on the nighttime histamine-driven surge in gastric acid secretion makes H2RAs an add-on therapy for patients with nighttime symptoms on PPI treatment such as nocturnal acid breakthrough (NAB). NAB is defined as a gastric pH < 4 for a period greater than 1 hour overnight in patients on twice-daily PPI therapy and occurs in more than 70% of patients on PPI therapy [33]. Addition of a nighttime H2RA to twice-daily PPI can reduce the percentage of NAB and lead to an improvement of nighttime reflux symptoms and sustained efficacy in short-term and long-term use [34, 35]. There are no significant differences between different H2RA agents in suppressing gastric acid, and different H2RAs are considered to have equivalent efficacy. At present, H2RAs are still popular over-the-counter medicines and widely used for controlling GERD symptoms because of their rapid onset of action [36].

**4.2. Proton Pump Inhibitor (PPI).** PPI blocks the gastric H<sup>+</sup>/K<sup>+</sup>-adenosine triphosphatase (ATPase) via covalent binding to cysteine residues of the proton pump to inhibit gastric acid secretion and is the most potent type of acid suppressants nowadays. Inhibition of H<sup>+</sup>/K<sup>+</sup>-ATPase is more effective than antagonism of H2R in suppressing gastric acid secretion because H<sup>+</sup>/K<sup>+</sup>-ATPase is the final step of acid secretion. Several trials and reviews have shown that PPIs are more effective in healing of erosive esophagitis and symptomatic relief than H2RAs [31, 37–39]. Eighty-three percent of patients with GERD symptoms and 78% of patients with erosive esophagitis have response to PPI treatment [40]. Many studies have evaluated the efficacy or superiority between different PPIs (esomeprazole, lansoprazole, pantoprazole, and rabeprazole) and, the results were inconsistent [41, 42].

Although PPI is the most successful acid suppressant in the treatment of GERD, unsatisfactory results still exist during PPI therapy. Fifty-nine percent of GERD patients with long-term PPI therapy still have persistent reflux symptoms [43]. About one-third of patients fail to adequately response to PPI therapy, and different groups of GERD, like erosive esophagitis, NERD, and Barrett's esophagus, have different response rates to PPI. NERD patients demonstrate the lowest

response rate to PPI, and PPI symptomatic response rate in NERD patients is only about 50–60% [43]. The definition of PPI failure is controversial, and refractory GERD is a term used to describe incomplete esophageal healing and/or unsatisfactory symptomatic response after a full course of PPI treatment. The mechanisms of failure of PPI therapy are complicated and multifactorial [44, 45]:

### Non-reflux-related causes

- Esophageal motility disorder, like achalasia, scleroderma
- Other esophagitis, like eosinophilic, pill, infection
- Functional heartburn or functional chest pain

### Reflux-related causes

- Compliance
- Rapid PPI metabolism (CYP2C19 polymorphisms)
- Nocturnal acid breakthrough
- Gastric acid hypersecretory states, like Zollinger-Ellison syndrome
- Anatomic abnormality, like large hiatal hernia
- Delayed gastric emptying
- Weakly acidic reflux
- Duodenogastroesophageal (bile) reflux
- Impairment of esophageal mucosal integrity
- Esophageal hypersensitivity
- Psychological comorbidity, like depression, anxiety, life stress
- Concomitant functional bowel disorder.

Traditional PPIs (omeprazole, lansoprazole, pantoprazole, rabeprazole, and esomeprazole) have relatively slow onset of action and provide insufficient 24-hour suppression of gastric acid under a once-daily dosage regime. Novel PPIs have been designed to improve the PPI efficacy with the advantage of rapid onset of action, extended-released profile, and longer half-life.

Tenatoprazole is a novel PPI characterized by an imidazopyridine ring in place of the benzimidazole moiety found in other proton pump inhibitors. Tenatoprazole has longer plasma half-life in comparison with other PPIs, providing a prolonged duration of acid inhibition and a shorter nocturnal acid breakthrough [46, 47]. Even though the plasma half-life of tenatoprazole is about seven times longer than that of other PPIs, tenatoprazole is considered a good alternative PPI for patients with ineffective once-daily PPI therapy [48]. However, the real efficacy of tenatoprazole on patients with GERD needs further investigation because most clinical trials have been performed in healthy volunteers. On the other hand, dexlansoprazole MR is a modified release formulation of dexlansoprazole and has a unique dual delayed-release formulation, which results in a dual-peak time-concentration profile as opposed to the single peak seen with conventional

PPIs. The dual delayed-release technology, made by two types of granules containing Dexlansoprazole MR capsule, provides two distinct drug-release periods in the small intestine, which extends plasma drug concentrations and prolongs the therapeutic time [49]. In previous reviews, dexlansoprazole MR has shown its greater effect in healing of erosive esophagitis, maintenance of esophagitis healing, and relief of symptoms in NERD patients as compared with traditional delay-released (DR) PPI [50, 51]. However, the therapeutic potential of dexlansoprazole MR in refractory GERD patients needs further evaluation. The other potential benefits of dexlansoprazole MR used in GERD patients include greater dosing flexibility without regard to meals, effective control of nocturnal heartburn and GERD-related sleep disturbances, and less drug-drug interaction with clopidogrel as compared with omeprazole or esomeprazole [52–54]. A single-blind, multicenter study which enrolled patients taking twice-daily PPI for heartburn control evaluated the efficacy of once-daily dexlansoprazole MR 30 mg as a step-down therapy for twice-daily PPI. This trial demonstrated that heartburn remained well controlled in 88% of patients after step-down to once-daily dexlansoprazole MR 30 mg. However, this study did not compare the efficacy between once-daily dexlansoprazole MR and once-daily traditional PPI as step-down therapy in this patient group [55].

Traditional PPIs are DR PPI because they are acid-labile and need enteric coating to prevent degradation in the stomach, resulting in relatively slow onset of pharmacological action. Traditional PPIs require several doses to achieve adequate acid suppression but fail to achieve adequate 24-hour acid suppression, allowing nocturnal acid breakthrough. Unlike DR PPI, immediate-release (IR) omeprazole is a formulation of nonenteric-coated omeprazole combined with sodium bicarbonate, which protects omeprazole from degradation by gastric acid, and is characterized by more rapid onset of antisecretory action compared with DR PPIs. Based on administration time, IR omeprazole provides profound control of postprandial and nocturnal intragastric acidity. The faster action of IR omeprazole is not influenced by concomitant antacid or food, which attenuates the efficacy of traditional DR PPI on acid suppression [56]. A randomized study conducted in GERD patients with nocturnal symptoms showed that bedtime dosing of IR omeprazole provided significant faster control of nighttime gastric pH and decreased nocturnal acid breakthrough compared with esomeprazole and lansoprazole. IR omeprazole also provided better nocturnal gastric acid control than lansoprazole and comparable efficacy with esomeprazole, suggesting that immediate-release omeprazole may be useful in treating nighttime heartburn [57]. IR omeprazole also provides adequate control of daytime gastric acidity compared with traditional PPIs. Howden et al. evaluated 24-hour intragastric acidity in GERD patients treated with once-daily IR omeprazole and found that morning dosing of IR omeprazole achieved better control of 24-hour intragastric acidity than lansoprazole and pantoprazole [58]. Buffered esomeprazole is another IR formulation and is an oral preparation consisting of an inner core of nonenteric-coated esomeprazole. Buffered esomeprazole achieved significantly faster control of intragastric acidity

and higher 24-hour median intragastric pH compared with pantoprazole in healthy volunteers [59]. The advantages of buffered esomeprazole use in GERD patients need further evaluation.

Extended-release (ER) rabeprazole is designed to provide initial acid suppression similar to DR PPI and maintain the plasma exposure of PPI over a longer period, achieving sufficient duration of acid suppression over a 24-hour period. Each ER rabeprazole formulation contains a single rabeprazole enteric-coated DR tablet and multiple rabeprazole pulsatile-release tablets, with prolonged pharmacodynamics effect performed by releasing rabeprazole in the intestine and colon separately. A study conducted in healthy volunteers showed that once-daily ER rabeprazole demonstrated a significantly longer gastric acid suppression (mean percentage of time with gastric pH > 4) over a 24-hour period compared with esomeprazole 40 mg and standard DR rabeprazole 20 mg, and formulations containing 50 mg ER rabeprazole showed the best pharmacodynamics profile compared with other dosages [60]. ER rabeprazole 50 mg once daily is as effective as esomeprazole 40 mg once daily in healing moderate-to-severe erosive esophagitis and heartburn resolution in a combined analysis of two studies, and the subgroup analysis suggests a better healing rate of severe esophagitis in an ER rabeprazole group [61].

VECAM is a combination of a PPI and succinic acid (an acid pump activator that has the same acid-stimulating activity as pentagastrin) and has a meal-independent antisecretory effect. Coadministration of succinic acid with PPI resulted in augmented PPI effects in animal models. A recent study that evaluated efficacy of once-daily VECAM and omeprazole in healthy volunteers showed that VECAM was significantly better in maintaining intragastric pH > 4 during the nighttime than omeprazole 20 mg, which may provide a therapeutic gain in nocturnal symptom control [62].

Long-term use of PPI as maintenance treatment raises the concern of long-term safety of PPI use. Several studies suggest that PPI use may be associated with osteoporotic fractures, enteric infections, community-acquired pneumonia, benign fundic gland polyps, malabsorption of calcium, magnesium, vitamin B12, and iron and decreasing efficacy of clopidogrel. However, most of these results came from observation in epidemiologic case-control studies, and many confounders may contribute to these associations. To date, the evidence of serious side effects from long-term PPI use is poor, and absolute risk of complications attributed to PPIs is low [63, 64].

**4.3. Potassium-Competitive Acid Blocker (P-CAB).** Potassium-competitive acid blockers (P-CABs) are another class of acid suppressants developed in the last few years and inhibit proton pumps via a different mechanism than PPIs. By competing with binding of the potassium-binding site of proton pump, P-CABs reversibly inhibit gastric  $H^+/K^+$ -ATPase and do not require acidactivation, which means that they are mealtimeindependent in contrast to PPIs. P-CAB is absorbed very quickly and provides rapid and profound acid suppression by achieving peak plasma concentration rapidly. Several P-CABs such as revaprazan (YH1885), soraprazan,

and AZD0865 have been evaluated in animal model and healthy volunteers, and these results have suggested that this group of acid suppressive drugs has a much faster onset of action and may provide greater acid suppression than conventional PPIs [65–67]. However, initial clinical trials with AZD0865 did not show better results than conventional PPI in GERD treatment. In treatment of erosive esophagitis, AZD0865 once daily only provided similar efficacy to esomeprazole 40 mg once daily in healing and controlling symptoms of erosive esophagitis [68]. In another clinical trial of AZD0865 and esomeprazole for the treatment of patients with NERD, AZD0865 also failed to demonstrate better heartburn control than esomeprazole in patients with NERD [69]. Liver toxicity was also observed in several P-CABs during early stages of drug development.

TAK-438 is a new type of P-CAB developed recently and has a slower dissociation rate from proton pumps than other P-CABs by higher pKa. In animal studies, TAK-438 showed a more potent and longer-lasting antisecretory effect than lansoprazole and other P-CABs [70–72].

## 5. Therapy Focused on TLESR

TLESRs are defined as periods of spontaneous, simultaneous relaxation of the lower esophageal sphincter and crural diaphragm. Reflux of gastric content during TLESRs causes reflux symptoms, and TLESRs are the main mechanism of all types of gastroesophageal reflux, including acid and nonacid reflux episodes [73]. TLESRs are primarily triggered by gastric distension through a vagovagal reflex initiated by activation of mechanoreceptors in the cardiac of stomach [74]. Several pharmacologic agents, including nitric oxide synthase inhibitors, cannabinoid agonists (CB1 receptor agonists), cholecystokinin receptor 1 (CCK1) antagonists,  $\gamma$ -aminobutyric acid type B (GABA<sub>B</sub>) receptor agonists, and metabotropic glutamate receptor 5 (mGluR5) antagonists, have been developed as TLESR reducers. However, some of these compounds did not provide clinically relevant effect and demonstrated undesirable pharmacologic side effects in clinical trials. At present, only GABA<sub>B</sub> receptor agonists and mGluR5 antagonists have reached the stage of clinical use and are the most promising agents of TLESR reduction [75].

**5.1. GABA<sub>B</sub> Receptor Agonists.** GABA<sub>B</sub> receptors are located at many sites within the central and peripheral nervous systems. GABA, as a major inhibitory neurotransmitter within the central nervous system, controls TLESRS by GABA<sub>B</sub> receptors expressed in LES-projecting neurons of the vagal nerve and the subnucleus centralis of the nucleus tractus solitarius. Other than effect from central nuclei, peripheral GABA<sub>B</sub> receptors also have inhibitory effect on gastric vagal mechanoreceptors and gastric distention-related TLESRs [76].

Baclofen, usually used in the management of spasticity, is a prototypical GABA<sub>B</sub> agonist and has effects in the control of TLESRs, initially noted in animal and healthy human studies [77, 78]. In patients with GERD, baclofen significantly decreases the number of reflux events and reflux symptoms

by reducing the incidence of TLESRs [79–81]. The effect of baclofen is also seen in patients with hiatal hernia [79]. In addition to control of acid reflux, baclofen also has inhibitory effect on nonacid and duodenal reflux as well as associated symptoms, suggesting a potential role of baclofen as add-on treatment in the management of refractory GERD [82, 83]. In recent studies, baclofen is also effective in attenuating extraesophageal symptoms of GERD. A study of patients with nighttime heartburn showed that baclofen reduced the number of reflux events during sleep and significantly improved sleep quality [84]. In a case series study enrolling three patients with refractory chronic cough due to GERD and being nonresponsive to PPI, baclofen 20 mg three times a day was given to substitute for domperidone and the cough was resolved after a 2–4-week course of baclofen in all patients [85]. Although baclofen is a promising agent of GABA<sub>B</sub> agonists in the management of GERD, the routine usage of baclofen in clinical practice is limited because of poor tolerability due to central nervous system-related side effects, such as weakness, drowsiness, confusion, dizziness, headache, and trembling. In an attempt to overcome these limitations, other GABA<sub>B</sub> agonists, such as arbaclofen placarbil or lesogaberan have been developed to improve tolerability.

Arbaclofen placarbil is an actively transported prodrug of the active R-isomer of baclofen and is efficiently absorbed throughout the intestine and colon, which allows it to be developed in a sustained release formulation. Arbaclofen placarbil has lower dosing frequency and more stable plasma concentration compared with baclofen to improve the safety profile [86]. A study to evaluate arbaclofen placarbil as monotherapy in 44 patients with GERD demonstrated that arbaclofen placarbil 60 mg once daily significantly decreased the number of reflux episodes and number of reflux-associated heartburn events over a period of 12 hours compared with placebo. Arbaclofen placarbil also provides a favorable tolerability and safety profile in this study [87]. However, arbaclofen placarbil was not superior to placebo in relieving heartburn in a subsequent randomized, double-blind, placebocontrolled trial of 156 patients with GERD [88]. Recently, no further studies with arbaclofen placarbil in GERD have been reported, and further development of this agent seems to be stopped.

Lesogaberan, a GABA<sub>B</sub> agonist that does not cross the blood-brain barrier and mainly acts on peripheral GABA<sub>B</sub> receptors, is designed to overcome the side effects of baclofen. In healthy volunteers, lesogaberan significantly reduces the number of TLESRs by 36% and acid reflux episodes by approximately 44% and increases LES pressure by 39% compared with placebo [89]. These effects are also found in patients with reflux symptoms despite PPI treatment and lesogaberan being well tolerated [90]. Based on successful results mentioned above, lesogaberan was evaluated as an add-on to PPI therapy in patients with persistent GERD symptoms despite receiving PPI therapy in the following two double-blinded, placebo-controlled, randomized studies. In a phase IIa study with a total of 244 randomized patients, 232 adult patients (114 lesogaberan- and 118 placebo-treated) received either lesogaberan (65 mg twice daily) or placebo in addition to PPI therapy for a period of 4 weeks and were analyzed for

efficacy. Treatment with lesogaberan, compared with placebo, resulted in increasing proportion of responders from 8% to 16% and increasing proportion of symptom-free days from 23% to 37% in heartburn and from 25% to 38% in regurgitation [91]. A recent dose-finding phase IIb study was conducted in 661 patients with partial response to PPI therapy, and persistent GERD symptoms demonstrated that lesogaberan at a dose 240 mg twice daily in addition to PPI was found to achieve a statistically significant response compared with placebo (26.2% versus 17.9%,  $P < 0.1$ ). The major side effect noted in this study was reversible elevated alanine transaminase levels (1.1%) [92]. The aforementioned studies demonstrate a relatively modest therapeutic effect of lesogaberan, yet this is insufficient for lesogaberan to be considered as a treatment option for refractory GERD. Further development of this compound was terminated.

**5.2. mGluR5 Antagonists.** Glutamate is the primary neurotransmitter involved in signalling from visceral and somatic primary afferents to the central nervous system. Peripherally located mGluR5 receptors have been associated with control of TLESRs, noted by animal studies initially, and mGluR5 antagonists are considered as potential therapy for patient with GERD [93].

ADX10059 is a potent selective negative allosteric modulator of the mGluR5 and is the most extensively studied agent of mGluR5 antagonists. In the first proof-of-concept study, two groups of 12 patients with GERD demonstrated ADX10059 250 mg three times daily significantly reduced esophageal acid exposure and symptomatic reflux episodes and were welltolerated [94]. A modified release (MR) formulation of ADX10059 had been tested in healthy volunteers, and ADX10059 MR 125 mg twice daily significantly decreased postprandial weakly acidic reflux episodes and esophageal acid exposure [95]. In a larger randomized clinical trial involving 103 patients with GERD, ADX10059 120 mg twice daily as monotherapy for 2 weeks significantly increased GORD symptom-free days and heartburn-free days, reduced antacid use, and improved total symptom score compared with placebo. ADX10059 was well tolerated and common adverse events in this study were mild-to-moderate dizziness and vertigo [96]. Despite good safety and tolerability in these short-term trials, further development of ADX10059 has been halted because of high incidence of adverse hepatic effects in a large multicenter trial of ADX10059 in migraine patients.

AZD2066 is a novel elective, noncompetitive antagonist of mGluR5 and has been studied in healthy volunteers. In a randomized crossover study, AZD2066 significantly reduced TLESRs and reflux episodes in healthy volunteers and had acceptable safety and tolerability profile [97]. The efficacy of AZD2066 in the management of GERD needs further investigation.

## 6. Therapy Focused on Gastroesophageal Motility

Function of gastroesophageal motility is an important factor influencing the pathophysiology of GERD, and disordered gastroesophageal motility includes reduced LES pressure,

ineffective esophageal motility, and delayed gastric emptying [98]. Prokinetic agents are a heterogeneous class of compounds acting on different receptors, including 5-hydroxytryptamine<sub>4</sub> (5-HT<sub>4</sub>) receptor agonists, dopamine<sub>2</sub> (D<sub>2</sub>) receptor antagonists, and motilin and ghrelin receptor agonists, and these compounds are proposed to improve GERD symptoms by enhancing esophageal motility and gastric emptying. However, prokinetic agents are usually not highly selective and provide off-target effects, which lead to controversial therapeutic benefits and undesirable side effects. Metoclopramide (D<sub>2</sub> antagonist), domperidone (dopamine antagonist), cisapride (5-HT<sub>4</sub> agonist) and tegaserod (5-HT<sub>4</sub> agonist) were usually used in patients with GERD in the past, but routine use of these agents was not suggested by guidelines because of limited benefits and high side-effect profile [40]. Erythromycin and ABT-229 are motilin receptor agonists, which are proposed to accelerate gastric emptying and increase LES pressure, and are still not routinely used as prokinetics in GERD because of several limitations [99]. Prokinetic agents are usually used in combination with acid suppression agents as an adjunctive, rather than as sole treatment of GERD.

**6.1. Mosapride and Itopride.** Mosapride, a prokinetic with selective 5-HT<sub>4</sub> receptor agonist and weak 5-HT<sub>3</sub> receptor antagonist actions, is effective in reducing acid reflux in the esophagus by improving esophageal motility and gastric emptying. Furthermore, mosapride is well tolerated and no serious adverse events are reported [100]. Mosapride is less effective than PPI as monotherapy in the management of GERD and is usually used as an adjunct to PPI therapy. Coadministration of mosapride has favorable influence on pharmacokinetics of PPI by accelerating the absorption of PPI and increasing maximum plasma concentration and the area under the time-plasma concentration curve and combination therapy with mosapride and PPI increases intragastric pH more rapidly than using PPI alone [101, 102]. However, mosapride as add-on therapy to PPI in patients with erosive esophagitis fails to provide better symptom relief than placebo, and additional benefits of mosapride are only possibly seen in patients with severe symptoms [103]. A double-blind, placebocontrolled study with mosapride in NERD patients demonstrated that addition of mosapride to PPI was not more effective than placebo in improving reflux symptoms [104]. In another study investigating efficacy of mosapride as add-on therapy to omeprazole in PPI-resistant NERD patients, improving reflux symptoms and gastric emptying was found in patients with delayed gastric emptying [105]. A recent small study showed that the addition of mosapride to esomeprazole improved esophageal peristaltic function in patients with GERD, but treatment response was not different between mosapride and placebo groups. Moreover, in the same study, better response seemed to be found in patients with dyspepsia than in those without dyspepsia [106]. Mosapride may provide additional benefit as add-on therapy in some special groups like those with motility disorder, rather than the general population.

Itopride, a D<sub>2</sub> antagonist with anticholinesterase activity, accelerates gastric emptying through both antidopaminergic

and anticholinesterase actions. It is usually used in the treatment of patients with functional dyspepsia and has good efficacy in postprandial fullness and early satiety. A pilot study conducted in 26 patients with GERD symptoms showed that itopride 100 mg three times a day improved GERD symptoms and decreased esophageal acid exposure, and no serious adverse events were noted [107]. However, recent mechanistic studies demonstrated that itopride had no significant influence on gastric emptying, esophageal peristaltic function, and LES pressure. Therapeutic benefit of itopride may come from influence on brain-gut correlation, visceral hypersensitivity, gastric accommodation, distension-induced adaptation, and TLESRs [108, 109]. Itopride has also been used in patients with laryngopharyngeal reflux as an add-on therapy to PPI for extraesophageal symptoms, but itopride did not provide better efficacy than placebo, only accelerated improvement rate [110, 111].

**6.2. Rikkunshito (TJ-43).** Rikkunshito, a traditional Japanese medicine, is composed of eight crude herbs and is widely used in Japan for patients with various gastrointestinal symptoms such as anorexia, nausea, and vomiting. Rikkunshito ameliorates the effects of nitric oxide-mediated gastric function to improve gastric emptying; besides, it also increases ghrelin levels, a potent stimulant for gastric emptying and gastrointestinal motility [112]. Rikkunshito reduced distal esophageal acid exposure by improving esophageal acid clearance in a small study conducted in children with GERD [113]. In healthy volunteers, standard dose Rikkunshito has no significant influence on postprandial acid or nonacid reflux events and does not accelerate esophageal clearance time [114]. In a study with Rikkunshito as combination therapy with rabeprazole (10 mg/day) in patients with refractory GERD showing resistant symptoms after a 4-week course of rabeprazole, combination therapy had similar efficacy of symptom relief compared with double-dose rabeprazole. In this study, subgroup analysis demonstrated that combination therapy was more effective than double-dose PPI in male patients with NERD [115]. Furthermore, Rikkunshito has strong binding capacity of bile salts and adsorption of bile salt, giving it a potential role in the management of refractory GERD related to duodenogastroesophageal reflux, which deserves further evaluation [116].

## 7. Therapy Focused on Visceral Hypersensitivity

Visceral hypersensitivity has been suggested to be an important mechanism of refractory GERD in patients with NERD and functional heartburn. The pathophysiology of esophageal hypersensitivity is complex, and visceral hypersensitivity resulting from upregulation of nociceptive pathways by peripheral and central sensitization and psycho-neuroimmune interactions is proposed. Heightened perception threshold and response function for stimulus within physiology range, like weakly acidic, nonacidic, or bile reflux, cause chest pain, heartburn, or reflux symptoms in these patients [117, 118]. Furthermore, psychological comorbidity also influences GERD symptom burden and treatment

response to PPI [119]. Tricyclic antidepressants, trazodone, and selective serotonin reuptake inhibitors have been used as pain modulators to improve esophageal pain in patients with noncardiac chest pain [120]. Serotonin-norepinephrine reuptake inhibitor and theophylline also improve esophageal hypersensitivity in patients with functional chest pain [121, 122]. Although these pain modulators are used in low non-mood-altering doses, side effects are relatively common. At present, these visceral analgesics provide a therapeutic alternative for PPI failure patients as add-on therapy or monotherapy [120].

Transient receptor potential vanilloid 1 (TRPV1) is a polymodal receptor, sensitive to noxious heat, change in pH (acidosis and alkalosis), endovanilloids, and numerous pungent plant products such as capsaicin, piperine, and eugenol, and it can be both upregulated and sensitized during inflammation and injury via peripheral and central nervous pathways. Studies have demonstrated that TRPV1 is a critical channel for mediating thermal hyperalgesia from noxious heat stimulation in mice, and these results have generated great interest in developing TRPV1 antagonists as pain modulators [123]. AZD1386 is a new TRPV1 antagonist and currently under investigation for esophageal pain in humans. In healthy men, AZD1386 reduces the threshold of esophageal pain perception in response to heat, but not to acid, mechanical, or electrical stimulation, as compared with placebo. A rise in body temperature and feeling cold reported by volunteers were observed in an AZD1386 group in this study [124]. Another study with AZD1386 in NERD patients with insufficient response to PPI demonstrated that AZD1386 did not significantly change pain threshold for heat, mechanical or electrical stimulation [125].

## 8. Pharmacological Options for Refractory GERD

The mechanisms of refractory GERD are complicated, and clarification of the possible causes of PPI failure is important to deal with these patients. Compliance to therapy should be checked first by physician, and the presence of functional gastrointestinal disorders, psychological distress, functional heartburn, or other esophagitis not related to reflux should also be carefully evaluated in these patients.

With some proven benefits, switching to another PPI or doubling the PPI dose has become the most common therapeutic strategy for patients who failed PPI once-daily treatment in clinical practice. When prescribing high-dose PPI, the dose is given twice daily before breakfast and dinner to have better control of intragastric pH [45, 126]. Although new formulations of PPIs can provide more immediate, potent, or consistent acid suppression, the real efficacy of newer PPIs for refractory GERD is still limited. Alginate and H2RA provide additional benefit on symptom relief in patients with persistent symptoms despite PPI therapy and can be considered as add-on therapy for refractory GERD [25, 35]. Under the concern of tolerance, H2RA is suggested to be taken on demand or intermittently. Baclofen is the most promising agent of TLESR reducer, but routine use in patients with refractory GERD is not favored because of neurological

side effects. Mosapride may provide additional benefit as add-on therapy in patients with severe symptoms or gastroesophageal motility disorder [103, 105]. Rikkunshito is a potent prokinetic and can be used as add-on therapy to PPI [115]. The value of pain modulators in the management of refractory GERD needs further evaluation.

## 9. Conclusion

To date, PPIs are still the most effective therapeutic tool and should be suggested as mainstay of treatment in patients with GERD. If symptoms continue despite adequate PPI use, the poor compliance or inadequate dosing time should be excluded before diagnosing refractory GERD in patients with poor response to PPI. The causes of refractory GERD are complex, and symptoms from weakly acidic or nonacid reflux suggest that acid suppression cannot be the only solution for all patients with GERD. New PPI formulations and new acid suppressants, P-CABs, have not shown clinical superiority to current PPIs. Nevertheless, newer PPI formulations with longer duration of action provide additional benefit in patients with poor compliance or nocturnal symptoms. In addition to PPI, TLESR reducers have been considered as the most promising strategies in the management of GERD. However, the therapeutic gain of TLESR reducers observed in patients with GERD was relatively small. Prokinetics have potential role as add-on therapy to PPIs and may provide additional benefit in special groups. Pain modulators that attenuate esophageal hypersensitivity are in the early phase of development, and the efficacy as well as tolerability needs further investigation. Overall, the target population for these new therapeutic agents remains to be defined by future studies. Despite the well-established benefits of current PPIs in the management of GERD, unmet needs are still present and require further pharmacologic development to provide viable options for better GERD treatment.

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## Review Article

# Pharmacological Therapy of Gastroesophageal Reflux in Preterm Infants

**Luigi Corvaglia,<sup>1,2</sup> Caterina Monari,<sup>1</sup> Silvia Martini,<sup>1</sup>  
Arianna Aceti,<sup>1</sup> and Giacomo Faldella<sup>1,2</sup>**

<sup>1</sup> Neonatology and Neonatal Intensive Care Unit, S. Orsola-Malpighi Hospital, via Massarenti 11, 40138 Bologna, Italy

<sup>2</sup> Department of Medical and Surgical Sciences (DIMEC), University of Bologna, 40126 Bologna, Italy

Correspondence should be addressed to Luigi Corvaglia; [luigi.corvaglia@unibo.it](mailto:luigi.corvaglia@unibo.it)

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Although gastroesophageal reflux (GER) is a very common phenomenon among preterm infants, its therapeutic management is still an issue of debate among neonatologists. A step-wise approach should be advisable, firstly promoting nonpharmacological interventions and limiting drugs to selected infants unresponsive to the conservative measures or who are suffering from severe GER with clinical complications. Despite of this, a concerning pharmacological overtreatment has been increasingly reported. Most of the antireflux drugs, however, have not been specifically assessed in preterm infants; moreover, serious adverse effects have been noticed in association to their administration. This review mainly aims to draw the state of the art regarding the pharmacological management of GER in preterm infants, analyzing the best pieces of evidence currently available on the most prescribed anti-reflux drugs. Although further trials are required, sodium alginate-based formulations might be considered promising; however, data regarding their safety are still limited. Few pieces of evidence on the efficacy of histamine-2 receptor blockers and proton pump inhibitors in preterm infants with GER are currently available. Nevertheless, a significantly increased risk of necrotizing enterocolitis and infections has been largely reported in association with their use, thereby leading to an unfavorable risk-benefit ratio. The efficacy of metoclopramide in GER's improvement still needs to be clarified. Other prokinetic agents, such as domperidone and erythromycin, have been reported to be ineffective, whereas cisapride has been withdrawn due to its remarkable cardiac adverse effects.

## 1. Introduction

Gastroesophageal reflux (GER) is very frequent in preterm infants. The incidence in those babies born before 34 weeks of gestation approximately amounts to 22% [1]. In the preterm population GER should not be usually considered a pathological phenomenon, as it might be promoted by a number of physiological factors. Among these, are included the supine posture, which enhances the migration of liquid gastric content through the looser gastroesophageal junction, the immature esophageal motility, which leads to a poor clearance of refluxate, and, eventually, the relatively abundant milk intakes [2].

The linkage between GER, apneas [3] and chronic lung disease is still controversial [4, 5]. In few cases, however, GER may be associated to clinical complications as, for instance, feeding problems, failure to thrive, esophagitis, and lung aspiration [6], thereby lengthening the hospital stay [7].

The therapeutic management of GER is still debated. A step-wise approach, which firstly promotes nonpharmacological interventions such as body positioning, modification of feeding modalities, or milk thickening, is currently considered an advisable strategy to manage GER in preterm infants [3, 6], limiting drug administration to those infants who do not benefit from conservative measures or with clinical complications of GER [8].

In the last decades, a widespread use of empirical antireflux medications in preterm infants, both during hospital recovery and after discharge, has been reported [9]. Most of these drugs, however, have not been specifically studied in these patients; moreover, antireflux medications have been noticed to cause serious adverse effects. For instance, inhibitors of acid gastric secretion as histamine-2 receptor blockers and proton pump inhibitors (PPIs) have been recently associated with an increased incidence of necrotizing

enterocolitis (NEC) [10, 11] and infections [12], whereas a linkage between cisapride administration and QTc prolongation was previously established [13, 14]. Therefore, a careful balance between risk and benefits for each drug should be carried out before starting a pharmacological therapy.

We aimed to provide a complete overview on the pharmacological management of GER in preterm infants, analyzing the evidences currently available conceiving the most prescribed antireflux drugs: surface protective agents as alginate-based formulations, histamine-2 receptor blockers, proton pump inhibitors, and prokinetics.

## 2. Gastroesophageal Reflux: Pathogenesis

Gastroesophageal reflux is very common in early childhood, being particularly frequent among preterm infants [3]. Indeed, several promoting factors may contribute to trigger GER in this specific population [15]. Preterm infants characteristically show a short and narrow esophagus, subsequently resulting in a slight displacement of lower esophageal sphincter (LES) above the diaphragm [16]. As Henry previously disclosed [17], gastrointestinal motor innervation gradually develops as postmenstrual age (PMA) increases. Hence, a nonperistaltic esophageal motility is frequently observed in preterm infants, therefore resulting in a subsequent ineffective clearance of the refluxate from the esophageal lumen [18]. Additionally, esophageal and upper esophageal sphincter (UES) motor responses to an abrupt intraluminal stimulation (i.e., due to the refluxate of gastric content) have been shown to be incomplete before 33-week PMA [19].

Neonates are usually lying in the supine position, which may additionally lead to GER worsening as well as the relatively abundant milk intakes that elicit LES relaxation through the enhancement of gastric distension [2].

It has been previously demonstrated that the occurrence of transient LES relaxations (TLESRs) represents the main GER's pathogenic mechanism in preterm infants, being linked to the 92–94% of the overall GER episodes detected in this population [2]. Unexpectedly, no difference was observed in the frequency of TLESRs between healthy infants and those affected by gastroesophageal reflux disease (GERD); however, the latter were disclosed to have a significantly higher proportion of TLESRs associated with acid GER [2].

## 3. Gastroesophageal Reflux: Clinical Presentation

In early childhood, the occurrence of GER may vary within a wide range of clinical manifestations, being vomiting and regurgitations the most frequent nonpathological symptoms. Generally, healthy babies who are experiencing frequent regurgitations in the absence of clinical complications are commonly referred as “happy spitters” [20].

Other common but less specific symptoms are represented by irritability, sleep disturbances, feeding refusal, or unexplained crying [8], especially if associated with back arching [21]. In fewer, severe cases, GERD may be combined with the presence of spastic torticollis and dystonic body movements, outlining the so-called Sandifer syndrome [22].

Sometimes frequent regurgitations or vomiting may be complicated by failure to thrive, despite an adequate caloric intake; thus, diagnosis other than GER, as, for instance, cow's milk protein allergy (CMPA), should be carefully ruled out [3, 8, 23].

Furthermore, due to the higher risk of gastric content's aspiration, the occurrence of GER in the neonatal population may contribute to the development of wheezing or pneumonia [24], whereas its linkage with the chronic lung disease is still controversial [4, 5, 25].

With regard to the preterm population, the linkage existing between GER, apneas, and cardiorespiratory events represents an actual issue of debate. On one hand, Di Fiore et al. recently reported that the rate of cardiorespiratory events (CEs), defined as episodes of apnea, bradycardia, and desaturations, following GER in healthy preterm infants, is irrelevant when compared to the overall number of events recorded during a 12-hour plethysmographic and pH-MII monitoring [26]. Similarly, no temporal relationship has been previously observed neither between the occurrence of cardiorespiratory events and acid refluxes detected by a pH-probe [27], nor between apneas and GERs recorded by multiple intraluminal impedance (MII) monitoring [28].

Conversely, we have previously perceived an increased rate of apneas occurring within the 30 seconds following a GER episode [29]. Moreover, as we have subsequently shown [30], the number of apneas is significantly higher after non-acid GER episodes, which prevail in the early postprandial period [31], confirming Wenzl's previous findings [32]. In accordance with these results, neither thickened formulas [33] nor the administration of sodium alginate [34] was found to improve the rate of apneas in symptomatic preterm infants. Eventually, a significant temporal association between cardiorespiratory events and GER, particularly remarkable among obstructive apneas and MII-GER, has been recently reported by Nunez et al. [35] in a small cohort of both term and preterm infants. Even so, the analysis of pieces of current evidence conceiving the relationship between apneas and GER in preterm infants is partially affected by the small sample sizes and the relevant methodological differences, thereby leaving this issue unsolved.

## 4. Diagnostic Procedures

The presence of GER, generally suspected on the basis of suggestive clinical symptoms, might be confirmed and characterized by specific diagnostic investigations. Esophageal pH-metry is generally accepted as a standard technique for diagnosing GERD [6], enabling the detection of acid GER episodes, defined by the decrease of intraesophageal pH values below 4, and other parameters as, for instance, reflux index and symptom index. However, a relevant limitation of this technique is its capability of detecting only acid refluxes. Thereby, as the acidity of gastric juice is age-dependent [36] and milk feeds are reported to buffer gastric content's pH [31, 37], pH-metry might result to be flawed in the preterm population.

Multiple intraluminal impedance (MII) monitoring analyses the variations of esophageal electrical impedance

through multiple intraluminal electrodes [38]. Due to its specific ability to detect nonacid reflux events, MII monitoring is considered a sensitive diagnostic tool, particularly useful during the postprandial period or in other conditions in which the gastric content is mainly nonacidic [39].

A combined MII and pH monitoring allows to assess acid, weakly acid and alkaline reflux, proximal extent, and nature of the reflux episodes being gas, liquid, or mixed [31, 40, 41], thereby achieving a relevant diagnostic ability. Combined pH-MII has been recognized by the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) to be superior to pH monitoring alone for the evaluation of the temporal relation between symptoms and gastroesophageal reflux, particularly if nonacidic, and for the assessment of pharmacological antireflux therapy's effectiveness [23, 41]. Hence, combined pH-MII monitoring is progressively emerging as the best diagnostic choice for GER's detection in preterm infants.

Nonetheless, even if these diagnostic techniques are highly accurate in detecting reflux events, on the other hand the presence of a probe through LES could potentially contribute to trigger GER episodes [42]. Therefore, therapeutic decisions should be guided by the presence of clinical manifestations and not just on the basis of instrumental GER detection.

A reflux questionnaire aimed to guide pediatricians' decisions regarding GER's diagnosis and treatment was developed in 1993 by Orenstein et al. [43]. The need of simpler and less invasive tests for diagnosing GERD in the preterm population has recently led Birch and Newell [6] to design a similar reflux scoring system based on clinical observation, adapting the Orenstein's questionnaire for hospitalized preterm infants. As the authors noticed, however, this questionnaire could not supplant the need for standard diagnostic investigations; moreover, it needs to be largely validated before being recommended as a diagnostic tool.

## 5. Conservative Management

A step-wise therapeutic approach is advisable in the management of GER in preterm infants. Conservative management of GER should be considered the first-line treatment in symptomatic babies who are experiencing frequent vomiting and effortless regurgitations without significant clinical complications.

On the basis of current evidences, body positioning can be considered a well-established and safe treatment in preterm babies symptomatic for noncomplicated GER, both acid and nonacid [6]. A reduction of GER has been observed in left lateral and prone positions [44–46], whereas right lateral and supine positions were reported to worsen GER [47, 48]. However, due to the risk of sudden infant death syndrome (SIDS) associated to prone position [49], this measure should be restricted to hospitalized infants.

Furthermore, supplemental benefits can be attained by dietary changes as, for instance, the reduction of feeding flow rate [50] or the use of an extensively hydrolyzed formula

[51]. Feed thickening has been found to be almost ineffective in the preterm population [52, 53]. Besides, the concern of a possible association between milk thickening and the development of necrotizing enterocolitis has been raised [54, 55]. Eventually, it should be noticed that a worsening in acid GER's features has been reported after HM fortification [56], while evidences regarding the effect of nonnutritive sucking [57] and intragastric tubes [42, 49] are still limited and controversial.

## 6. Pharmacological Therapy

The provision of drugs in preterm infants with GER should be taken into account when conservative measures do not provide effective results on GER symptoms, or it might be considered at first instance in those symptomatic infants who are suffering from severe GER clinical complications, as failure to thrive, weight loss despite an adequate caloric intake, hematemesis, aspiration pneumonia, and Sandifer syndrome. We provide a comprehensive analysis of the currently available evidences, regarding the main antireflux medications administered in the neonatal population, with particular reference to preterm infants.

*6.1. Alginate-Based Formulations.* Alginate-based formulations, acting as a physical protection of the gastric mucosa, are commonly employed to treat GERD, both in adult and pediatric populations. In the presence of gastric acid, sodium alginate precipitates to form a low-density but viscous gel, while sodium bicarbonate, usually contained in these formulations, is converted to carbon dioxide. The latter is entrapped within the gel, forming a foam which floats on the surface of gastric content, preferentially moving into the esophagus instead of acidic gastric contents during GER episodes [58].

With regard to the pediatric population, the first placebo-controlled study, disclosing the effect of sodium alginate on vomiting and regurgitation in symptomatic infants and children, dates back to 1987 [59]. This finding has been subsequently confirmed in an open-label trial [60] testing a sodium alginate liquid formulation at daily doses of 1–2 mL/Kg. Moreover, these comforting data have been eventually proved by Miller [61], who studied a new aluminum-free formula of sodium alginate in infants with recurrent GER, compared to a placebo group.

On the contrary, Del Buono et al. [62] did not notice any difference in acid GER indexes between an alginate formula and placebo, except for the lower esophageal peaks reached by the refluxate. This opposite result might be explained by the use of a powder formulation, which did not contain bicarbonate, thus mainly exerting a thickening action rather than a buffering one.

Alginate-based formulations are reported to be the most commonly prescribed antireflux medications in preterm infants symptomatic for GER [1]. Despite of this, the evidences currently available on the efficacy and safety of sodium alginate in this specific population are still limited.

In a previous study [63] we have evaluated the effectiveness of a formulation containing sodium alginate and

sodium bicarbonate (Gaviscon Reckitt Benckiser Healthcare), administered 4 times a day at a dosage of 0.25 mL/kg, to improve many GER's features in preterm infants. Sodium alginate decreased the number of acid GER episodes and total acid esophageal exposure, detected by pH-monitoring. Moreover, it also reduced the number of refluxes reaching proximal esophagus, whereas it had no influence on nonacid refluxes, detected by MII.

The two substances contained in the formulation seem to work together as thickening and buffering factors, exerting a complementary effect in lowering acid GER's indexes. The efficacy of sodium alginate is particularly relevant in decreasing acid GER, which is known to be the most important determinant of GERD [2]. Additionally, due to the bicarbonate buffering effect, GER's pH may probably rise up.

Depending on its physical and chemical characteristics, GER may be classified into acid and nonacid. While the latter occurs in the early postprandial period, when the gastric fullness promotes the passage of gastric content into the proximal esophagus, the former occurs in the late postprandial period, when the stomach is partially empty, and it is suggested to represent the main trigger for reflux-related apneas [64]. The remarkable improvement in acid refluxes suggests that this preparation remains inside the stomach for quite a long period after feeding, also because of the longer time of gastric emptying of preterm infants.

As for safety, drugs containing sodium alginate have been linked to bezoar formation [65] and to adverse events due aluminum's toxicity [66, 67]. Furthermore, the content of sodium within this medication is quite high for preterm infants, thereby potentially leading to hypernatremia.

The results of our study are in agreement with those disclosed by Atasay et al. [68], who have evaluated the efficacy of a formulation containing sodium alginate and potassium bicarbonate, administered 4 times a day at a dose of 1 mL/kg in a cohort of 41 preterm infants with GERD. Eighty-three percent of the patients with pathologic GER responded to the therapy, showing a significant reduction of acid GER parameters and improving clinical features such as vomiting and weight gain. Moreover, the occurrence of possible side effects as abdominal distension, constipation, diarrhea, thickening of the stool, and anal fissure was also analyzed; none of these manifestations was noticed, except for stool thickening in three infants.

These encouraging but merely preliminary data should be deeply investigated in larger trials, in order to have a complete and faithful scenario particularly regarding the safety profile of sodium alginate in preterm infants.

As van den Anker [69] suggests in a recent comment on the study by Atasay et al. [68], this background is urgently needed before recommending the routine use of alginate-based formulations in this specific population.

**6.2. Histamine-2 Receptor Blockers.** Histamine-2 ( $H_2$ ) blockers are a group of drugs which compete with histamine for the selective linkage to the  $H_2$  receptor, placed in the gastric wall. This bond leads to a lowered secretion of the hydrochloric acid by the parietal cells in the stomach and, thus, to an increased intragastric pH [70].

Several reports support the effectiveness of  $H_2$ -blockers in children and infants affected by GERD and esophagitis [71–73].

Ranitidine is the main  $H_2$ -blocker used in Neonatal Intensive Care Units (NICUs). Like many other medications, it has not been approved by the Food and Drug Administration (FDA) for the use in the preterm population, being therefore prescribed in an off-label manner because of the perceived safety and potential benefits [9]. Ranitidine is frequently administered in a wide range of situations. It is usually employed either as prophylaxis and therapy in preterm infants with stress-induced gastric bleeding [74] or, mostly, in infants with GERD, despite the lack of high-level evidences supporting its efficacy. Ranitidine may be also administered in association with steroids, in order to minimize the risk of gastritis [70]. Nevertheless, the efficacy of  $H_2$ -blockers in the preterm population is still an issue of debate [9].

A research performed in critically ill term and preterm infants, aiming to establish the required optimal dose for these two different populations, proved that ranitidine at the dose of 0.5 mg/kg/twice daily effectively keeps gastric pH over 4 in preterm infants, whereas the optimal dose for term infants amounts to 1.5 mg/kg, three times a day [74]. After the first month of life, oral doses range between 2 and 5 mg/kg twice daily, whereas the intravenous dosage is reported to be 2–4 mg/kg/day, divided in 2 daily doses [75]. However, the chronic use of ranitidine is discouraged, due to the frequent development of tachyphylaxis within 6 weeks from the beginning of the therapy, which leads to a decline of its efficacy [8, 75].

With regard to the safety profile of  $H_2$ -blockers, numerous trials have investigated their short run effects on preterm infants [10–12], disclosing no encouraging results.

As a matter of fact, gastric juice, which is mainly composed by HCl and pepsin, is one of the most important nonimmune protection systems [76], which directly reduces intragastric bacterial proliferation and indirectly modulates the composition of the intestinal microflora [77]. HCl has a powerful bactericidal effect on the exogenous bacteria introduced into the stomach: at pH < 3, gastric juice is able to kill bacteria within 15 minutes [78]. According to this finding, a higher growth of pathogens in the gastroenteric tract has been associated to intragastric pH levels >4 in a cohort of preterm infants [79]. With regard to the effects of  $H_2$ -blockers on gut's bacterial colonization, a lowered fecal microbial diversity and a shift toward a Proteobacteria pattern have recently been disclosed by Gupta et al. [80], therefore potentially predisposing to NEC development.

The association of gastric acidity inhibitors, such as  $H_2$ -blockers, with a higher incidence of necrotizing enterocolitis and infections in very-low-birth-weight (VLBW) preterm infants represents the most daunting issue in the current literature.

Guillet et al. [10] performed a retrospective case-control study on VLBW infants to investigate the association between the incidence of NEC and the use of  $H_2$ -blockers, as ranitidine, famotidine, and cimetidine. A significant linkage has been proven, with an overall incidence of NEC of 7.1%. In

particular, the administration of these drugs started at a mean of  $18.9 \pm 15.5$  days before NEC development. These data have been recently confirmed by Terrin et al. [12], who have acquired information about VLBW infants from four different Italian NICUs. The patients were clustered into two different groups: infants treated with ranitidine as prophylaxis or treatment for stress-induced peptic disease or suspected GERD, and infants not exposed to this drug, as control cohort. According to their results, NEC was more frequent in infants treated with ranitidine (rate 9.8%) compared to those who did not receive it (rate 1.6%), although the risk of NEC was not associated neither with the dose nor with the duration of treatment. Moreover, the authors documented a higher rate of infections (overall infections, sepsis, pneumonia, and urinary tract infections) and fatal outcome in the treated VLBW infants.

The latest evidence on the linkage between  $H_2$ -blockers and NEC has been provided by Bilali et al. [81] in a case-control trial: the authors documented a higher incidence of NEC in preterm infants treated with ranitidine when compared to the control group (17.2% versus 4.3%, resp.).

Moreover, the provision of  $H_2$ -blockers has been reported to strike down several leukocyte's functions, thus leading to an insufficient control of the production of inflammatory cytokines in the intestinal tract [82, 83]. Therefore, the factors mentioned above contribute importantly to increase the risks of infections. According to these findings, Canani et al. [84] demonstrated a more frequent onset of infections in children aged 4–36 month, symptomatic for GERD, and treated with GA inhibitors. In particular, a significant higher rate of acute gastroenteritis and community-acquired pneumonia was observed. These findings were probably due to hypochlorhydria, induced by an 8-week treatment with ranitidine, at a daily dose of 10 mg/kg, or omeprazole, at a dosage of 1 mg/kg/day.

Stoll et al. [85] demonstrated an increased rate of bacteremia, late onset sepsis, and meningitis in VLBW treated with both  $H_2$ -blockers and postnatal steroids, in order to prevent the risk of gastrointestinal bleeding.

A previous analysis of the risk factors for the development of bloodstream infections in a cohort of both term and preterm newborn admitted to NICU registered a highly significant association with  $H_2$ -blockers' administration [86].

$H_2$ -blockers are probably overused in most of the NICUs to treat many clinical conditions, without any evidence of benefits, and mostly burdened by an adverse risk-benefits ratio.

**6.3. Proton Pump Inhibitors.** PPIs act as long-term blockers of the gastric proton pump, which catalyzes the final phase of the acid secretory process, hindering both basal and stimulated acid secretion by the parietal cells.

Data collected by MII in preterm and term infants with GERD showed that PPIs increase the esophagus baseline levels of impedance, which is known to be related to the esophageal mucosal integrity [87], suggesting an ameliorative effect.

The prescription of PPIs as therapeutic agents for the treatment of GERD in the pediatric population has largely

increased over the last 10 years, in particular after the therapeutic failure of  $H_2$ -blockers [88]. Currently available PPIs, however, are not approved for being prescribed below one year of life, with the exception of esomeprazole, which has recently gained the indication for the short-term treatment of erosive esophagitis in infants from 1 to 12 months of age.

Data on the safety and efficacy of PPIs in the preterm population are few and controversial. The effectiveness of omeprazole on preterm infants with GERD has been investigated by Omari et al. [89]. This drug, administered at a daily dose of 0.7 mg/kg, yielded a significant decrease of acid GER frequency and of the overall degree of esophageal acid exposure, which fell even below the currently defined normal levels. However, despite this clear pharmacodynamic effect, omeprazole appeared clinically ineffective to relieve GER symptoms, confirming the previous finding of a double-blind placebo-controlled trial, performed on infants aged 3 to 12 months [90].

Similarly, Orenstein et al. [91] assessed the efficacy of lansoprazole versus placebo on a large cohort of both term and preterm symptomatic infants, showing no significant advantage over placebo in the reduction of symptoms attributed to GERD (i.e., crying, regurgitation, refuse of feeding, back arching, wheezing, and coughing). Besides, a trend towards increasing serious adverse effects was reported in the lansoprazole group, regarding, in particular, lower respiratory tract infections. However, as the enrolled infants did not undergo a pH-MII evaluation, the authors hypothesized a causal role of predominant nonacid reflux events, for which PPIs are ineffective, on GER symptoms.

On the contrary, a recent study by Omari et al. [92], on the effectiveness of esomeprazole in preterm infants, demonstrated a significant decrease in the number of GERD-related symptoms, a remarkable reduction of the overall esophageal acid exposure and, as previously found [93], a lowered number of acid bolus reflux episodes whereas, as expected, nonacid GER features were not influenced. However, these results were not controlled for placebo effects; therefore, they should be confirmed in further placebo-controlled trials.

With regard to pantoprazole, a daily dose of 1.2 mg/kg has been recently reported to improve the frequency of acid GER as well as its mean clearance time in both term and preterm infants. Nonetheless, adverse effects were perceived in more than half of the cohort, being anemia, hypoxia, and constipation the most frequently observed [94, 95]. However, as preterm infants were not analyzed separately from term infants, the specific role of pantoprazole on this specific population cannot be currently ascertained.

PPIs are known to decrease gastric mucosal viscosity [96], to reduce gastrointestinal motility, and to delay gastric emptying [97], potentially enhancing the growth of pathogenic bacteria and leading to a disruption of gut microbiota [98]. Moreover, PPIs have been shown to inhibit neutrophils' chemotactic migration [99], to constrain their phagocytic activity [100], and to decrease the adherence of these cells to the endothelium [101], consequently leading to an increased risk of bacterial infections. According to the issues described so far, a higher incidence of intragastric bacterial infections [102] and community-acquired pneumonia has been

reported in association with PPIs' therapy [103]. As mentioned above, children with gastric acid suppression, induced both by PPIs and H<sub>2</sub>-blockers, showed a higher incidence of community-acquired pneumonia and gastroenteritis [84].

As asserted in a recent systematic review, a higher incidence of NEC has been reported in preterm VLBW infants in association with the suppression of gastric acidity, induced both by H<sub>2</sub>-Blockers and PPIs [11]. The state of gastric hypochlorhydria, induced by acid suppression, may allow bacterial survival, enhancing gut colonization and potentially leading to bacterial overgrowth, which is known to play an important role in the pathogenesis of NEC [80]. Additionally, it should be considered that gastric juice becomes more acid as gestational and postnatal age increases [36]. Therefore the administration of gastric acidity inhibitors in preterm infants, who already have a lower gastric acidity, will make them more susceptible to bacterial overgrowth, potentially enhancing the risk of NEC development.

So far, it is not possible to fit these evidences specifically for PPIs, as data currently available on the occurrence of NEC and infections are jointly concerning both PPIs and H<sub>2</sub>-blockers.

Hence, further systematic and controlled assessments should be carried out to clarify the clinical efficacy of PPIs on GERD's symptoms and their safety in the preterm population. On the basis of the present evidences, pharmacological therapy with PPIs seems to result in an adverse benefit-risk balance; therefore, it is not routinely recommended in preterm infants with symptomatic GERD.

**6.4. Prokinetic Agents.** Promotility agents (cisapride, metoclopramide, erythromycin, and domperidone) belong to a family of drugs which have been widely employed in pediatric practices, in order to reduce the symptoms of GER [104].

In particular, these drugs seem to improve gastric emptying, to reduce emesis, and to enhance LES tone, thus allowing to treat clinical features of GER [105].

**6.4.1. Cisapride.** Cisapride is the most largely investigated prokinetic drug, being used as a treatment of GER in adults, children, and neonates.

Cisapride is able to enhance the release of acetylcholine from the mesenteric plexus [13], therefore decreasing GER. However, this medication seems to be an important antagonist of the rapid component of the delayed rectifier current of potassium in cardiac cells, thus acting as a III class antiarrhythmic medicament [13, 105].

The clinical efficacy of cisapride in reducing GER in preterm infants has been demonstrated by Ariagno et al. [106]. The authors found a significant reduction in reflux indexes and in the number of GER episodes lasting more than 5 minutes, whereas the therapy was ineffective on the total number of refluxes/24 hours and on the duration of the longest episode.

On the contrary, McClure et al. [107] raised concerns on the efficacy of cisapride in preterm infants, as it was observed to cause a delay in gastric emptying, which led to an amplification of refluxes and their symptoms. Therefore,

the authors did not recommend its use in this particular population.

As the metabolism of cisapride occurs through the cytochrome P 450 (CYP 450) system, which is not fully developed in preterm infants, the simultaneous provision of other drugs inhibiting the CYP 450, such as azole antifungals and macrolides, may further reduce cisapride clearance, increasing its serum levels and, therefore, resulting in a major toxicity [13, 106].

Due to its cardiac effects, the relationship existing between the administration of cisapride in preterm infants and the prolongation of QTc interval has been deeply investigated.

A prolongation of QTc interval in infants and children receiving cisapride has been previously reported by several authors [108, 109]. Semama et al. [110] confirmed a significant increase in the QTc interval in a cohort of term infants treated with cisapride at the dose of 0.2 mg/kg 4 times a day; in particular, the prolongation of the interval resulted to be dose dependent, probably due to the immaturity of liver enzymes which leads to an accumulation of cisapride.

With regard to the preterm population, as Dubin et al. have demonstrated, 48% of the infants treated with cisapride developed anomalies of repolarization; QTc values were significantly longer, especially in babies with gestational age lower than 32 weeks [13].

In a previous study [14], we have examined the possible existence of a relationship between fetal growth and QT prolongation, in a cohort of preterm infants receiving cisapride compared to a control group. In relation to the fetal growth pattern, the infants enrolled were classified as adequate-for-gestational-age (AGA) or small-for-gestational-age (SGA). Both baseline QTc and in-treatment QTc were significantly higher in the SGA group when compared to the values of AGA infants. Therefore, according to these results, intrauterine growth retardation might represent a risk factor for cisapride-induced QT interval's prolongation in preterm infants.

Hence, due to the possible cardiac toxicity of cisapride and the increased risk of potentially lethal cardiac arrhythmias or sudden death, cisapride has been gradually withdrawn [111], and it is no longer an approved therapy for GER.

However, if an isoform of this medicament, which has no cardiac side effects, becomes available, more detailed studies should be initiated, in order to investigate the real effects of cisapride on GER and its clinical features.

**6.4.2. Domperidone.** Domperidone is a peripheral dopamine D<sub>2</sub>-receptor antagonist, commonly provided to treat regurgitation and vomiting. As a matter of fact, it is able to enhance motility and gastric emptying and to reduce postprandial reflux time [112].

To date, there are few evidences of its efficacy in infants and children with GERD [113, 114], and none in preterm infants [6]. In their review dated 2005, Pritchard et al. [112] demonstrated no convincing efficacy of domperidone in the treatment of GER or GERD in young children, mainly because of several limitations, such as the small number of trials or the high methodological heterogeneity in the

studies analyzed. In fact, domperidone does not seem to be more effective in improving symptoms of GER compared to placebo [113]. Recently, Scott [114] confirmed the above mentioned findings, showing little convincing evidence for the efficacy of domperidone in infants with GER. A recent study by Cresi et al. [115] aimed to assess the effectiveness of domperidone on both term and preterm infants symptomatic for GER. The authors showed a paradoxical increase in the number of GER episodes as well as a reduction of their duration, whereas no effects were found in height and pH of refluxes. As hypothesized by the authors, domperidone may amplify the motor incoordination of neonatal gastroesophageal tract. Therefore, the efficacy of this drug in the management of neonatal GER still appears controversial.

Despite no side effects have been reported in all the four trials, domperidone might provoke serious neurologic symptoms, such as extrapyramidal symptoms, oculogyric crises, and long-term hyperprolactinemia [112]. The pediatric population is particularly susceptible to these problems, due to an immaturity of the nervous system and blood-brain barrier.

Moreover, domperidone, such as cisapride, is metabolized by the cytochrome P450; the immaturity of this system, or the simultaneous provision of drugs, which may inhibit its functionality, may lead to higher concentrations of this medicament, consequently enhancing its toxicity.

**6.4.3. Erythromycin.** Erythromycin, a common used macrolide antibiotic, acts as a strong nonpeptide motilin receptor agonist that contributes to enhance gastric emptying and induces phase III activity of the interdigestive migratory motor complex (MMC), propagating from the stomach to the ileum [116]. Erythromycin increases the release of endogenous motilin and stimulates cholinergic nerves of the gastrointestinal tract, thus resulting in a major release of calcium and in the contraction of muscles of the gut [117].

Oral erythromycin has been proposed as a rescue medication for feeding intolerance [118]. Specifically, three different oral doses have been investigated: a high dose (12.5 mg/kg administered 4 times a day for an overall period of 14 days) [116], an intermediate dose (10 mg/kg administered 4 times a day for 2 days followed by 4 mg/kg 4 times a day for the next 5 days) [119], and finally a low dose (6–15 mg/kg/die) [118, 120]. Although an improvement of gastrointestinal dysmotility, as well as a reduction of days gained to establish an adequate enteral nutrition, has been reported in these trials, the action of erythromycin in promoting enteral feeding appears to be dose as well as age-dependent. In fact, a decrease of the effectiveness of this medication has been observed in the more preterm infants (<32 weeks of gestational age), probably due to gut immaturity [117].

Recently, a large randomized controlled trial demonstrated in a preterm cohort a significant improvement on parenteral-nutrition associated cholestasis [121]. This finding may be justified by the quicker attainment of full enteral feeding, at the intermediate-dose of erythromycin (5 mg/kg 4 times/day for 14 days), therefore resulting in a shorter duration of parental nutrition [121, 122]. Regarding the erythromycin's effectiveness on GER, one of the mentioned

trials [116], performed in a small number of preterm infants, reported no significant improvement in GER indexes after the low-dose provision.

Possible adverse effects have been observed in relation to erythromycin's administration. Among them, an increased risk of infantile hypertrophic pyloric stenosis has been reported, especially in association to an early use, that is, during the first 2 weeks of life [123]. Moreover, cardiac arrhythmias have been related to erythromycin's intravenous administration [124].

**6.4.4. Metoclopramide.** Metoclopramide is a dopamine agonist, which improves the responses of the upper gastrointestinal tract to acetylcholine [125]. Moreover, metoclopramide has been previously shown to enhance LES tone [126].

Therefore, thanks to its promotility properties, metoclopramide has been widely used as treatment of GERD in infants and children, despite the lack of rigorous evidences approving its usage [127].

Because of its widespread employment and an increasing number of concerns about its toxicity in infants, Hibbs and Lorch [127] carried out a systematic review regarding the provision of metoclopramide for GERD in infants aged 0 to 23 months. Twelve studies, testing metoclopramide at doses ranged between 0.1 and 1 mg/kg, were evaluated. Conversely to a Cochrane review published in 2004 [128], which affirmed the effectiveness of metoclopramide in reducing both clinical symptoms and reflux indexes in infants with GERD, the conflicting results of the studies and the lack of a valid demonstration of the metoclopramide's efficacy or toxicity did not allow the authors to assess a risk-benefit profile of metoclopramide in infants affected by GERD. However, only few studies evaluated in this review had been performed in the preterm population.

Another trial performed in preterm infants regarding metoclopramide's effectiveness failed to demonstrate the improvement of bradycardia clinically attributed to GER [129].

Eventually, metoclopramide's administration might be associated to adverse effects [130]; particularly, irritability was the most frequent side effect, followed by dystonic reactions, drowsiness, oculogyric crisis, emesis, and, eventually, apnea.

Therefore, the current literature is insufficient to either support or contrast the employment of metoclopramide in the usual GERD's treatment.

## 7. Conclusions

Although GER is a very common condition among preterm infants, its therapeutic management in this peculiar population still remains controversial.

A step-wise therapeutic approach, primarily based on nonpharmacological strategies, should be advisable in the management of preterm infants affected by noncomplicated clinical GER, especially in the so-called "happy spitters" [8]. When conservative measures do not provide effective results, or in the presence of clinical complications, the provision of a pharmacological therapy should be considered.

Although the empirical prescription of antireflux drugs in preterm infants affected by GERD is widespread [9], the overall available evidences regarding the efficacy and the safety of antireflux drugs in the preterm population are quite limited. As a matter of fact, most of these medications have not been neither assessed nor approved for being used in preterm infants. Additionally, serious side effects have been reported in association to their provision.

On the basis of preliminary results, alginate-based formulations might be considered a promising treatment of GERD, both buffering the gastric content and physically hampering the refluxate. However, further trials are advisable in order to confirm these findings and, in particular, to test out the safety of these medications before recommending their routine use. With regard to inhibitors of gastric acidity, as H<sub>2</sub>-blockers or PPIs, evidences conceiving their effectiveness in preterm infants with GERD are limited. Furthermore, a significantly increased risk of NEC and infections has been noticed, therefore leading to an unfavorable risk-benefit ratio. Due to conflicting evidences, the efficacy of metoclopramide in GERD's improvement is still controversial. Other prokinetic agents, such as domperidone and erythromycin, have been reported to be ineffective, whereas cisapride, largely used to treat GERD in the preterm population up to a decade ago, has been withdrawn due to its remarkable cardiac adverse effects.

Hence, to avoid a harmful overtreatment in the preterm population, pharmacological therapy should be limited to selected infants suffering from GER complications or after the failure of the conservative management. Finally, the therapeutic choice among the several antireflux medications currently available should represent the result of a careful and targeted risk-benefit balance.

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## Review Article

# Surgical Management of Pediatric Gastroesophageal Reflux Disease

Hope T. Jackson<sup>1</sup> and Timothy D. Kane<sup>2,3</sup>

<sup>1</sup> Department of Surgery, The George Washington University School of Medicine & Health Sciences, Washington, DC, USA

<sup>2</sup> Division of Pediatric Surgery, Department of Surgery, Sheikh Zayed Institute for Pediatric Surgical Innovation, Children's National Medical Center, Washington, DC, USA

<sup>3</sup> Surgical Residency Training Program, Children's National Medical Center, Division of Pediatric Surgery, 111 Michigan Avenue, NW Washington, DC 20010-2970, USA

Correspondence should be addressed to Timothy D. Kane; [tkane@cnmc.org](mailto:tkane@cnmc.org)

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Gastroesophageal reflux (GER) is common in the pediatric population. Most cases represent physiologic GER and as the lower esophageal sphincter (LES) matures and a solid diet is introduced, many of these patients (>65%) experience spontaneous resolution of symptoms by two years of age. Those who continue to have symptoms and develop complications such as failure to thrive, secondary respiratory disease, and others are classified as having gastroesophageal reflux disease (GERD). Goals of GERD treatment include the resolution of symptoms and prevention of complications. Treatment options to achieve these goals include dietary or behavioral modifications, pharmacologic intervention, and surgical therapy. This paper will review the clinical presentation of GERD and discuss options for surgical management and outcomes in these patients.

## 1. Introduction

Gastroesophageal reflux (GER) is a common and often benign occurrence in the pediatric population that refers to the regurgitation of gastric contents into the esophagus. The majority of these patients (>65%) will experience spontaneous resolution of their symptoms by two years of age [1–3]. Those who continue to have symptoms and develop complications such as failure to thrive, secondary respiratory disease, laryngospasm, esophagitis, and esophageal strictures are classified as having gastroesophageal reflux disease (GERD). The overall goals for the treatment of GERD are to relieve symptoms, maintain remission of symptoms, and manage or prevent complications. Treatment options to achieve these goals include dietary or behavioral modifications, pharmacologic intervention, and surgical therapy. Increased understanding of GERD pathophysiology has led to improved diagnostic techniques, pharmacologic agents, and invariable approaches to surgical management [4]. This paper will review the classification of physiologic and pathologic GER and clinical presentation and diagnosis of GERD

as well as discuss options for surgical management and outcomes in these patients.

## 2. Classification

*2.1. Physiologic GER and Pathologic GER/GERD.* Up to 60% of healthy infants 0–6 months of age experience occasional refluxing of gastric contents into the esophagus. This percentage declines to 5% at one year of age [5]. The mechanism of reflux is believed to be due to an immature lower esophageal sphincter (LES) and a predominately liquid diet and it is considered physiologic. As the LES matures and solids are introduced into the diet, reflux resolves, typically by 12 months of age [6]. Those children who do not experience resolution of their reflux may go on to develop GERD which describes the complications that can result from persistent GER (i.e., secondary respiratory disease, apnea, acute-life threatening events (ALTE), and esophageal stricture). The pathophysiology of GERD is believed to have anatomical (short esophagus, stricture, and hiatal hernia) and/or

TABLE 1: Common symptoms of infant and adolescent patients presenting with GERD [8].

Infants	Older children and adolescents
Regurgitation and vomiting	Hoarseness
Feeding difficulties and feeding refusal	Chronic cough
Failure to thrive	Epigastric pain and irritability
Apnea or apparent life-threatening event (ALTE)	Dysphagia
Sandifer syndrome or spasmodic torsional dystonia [8] (arching of the back and neck (Sandifer posturing) and abdominal wall contractions)	Bronchospasm and asthma

functional components (pharmacologic agents, poor dietary habits, and abnormal gastric motility) [7].

### 3. Clinical Presentation/Diagnosis

The clinical symptoms of reflux that lead to GERD may vary according to the age of the child. Infants commonly present with regurgitation, vomiting, and irritability while the older child or adolescent may more commonly present with dysphagia, epigastric/substernal pain, and heartburn [17]; see Table 1. Management of GERD in both adults and children is based on disease severity, the degree of symptoms, and presence or absence of complications of GER determined by diagnostic evaluation [4]. Given these variables, it is no surprise that GERD is rarely diagnosed solely on the basis of one diagnostic test, but usually a combination of studies. While GERD can be diagnosed by typical history and physical examination findings as a basis for a trial of therapy, typical symptoms are not always present and do not always predict which patients will respond to treatment. See Table 2 for the most commonly used diagnostic tests in the evaluation of GERD.

### 4. Management

The management of children with GERD initially begins with nonoperative measures that often result in resolution of symptoms. The goals of medical management include lifestyle modifications, acid-suppressive medications designed to alter gastric pH, and prokinetic agents that seek to improve the transit of gastric contents. Lifestyle modifications consist of formula changes and thickened feeds in infants and reduced caffeine intake and weight reduction in adolescents. Adolescents also make up a portion of the smoking population. While pediatricians should counsel against smoking and advocate for cessation regardless of the presence of GERD, it

TABLE 2: Most commonly used diagnostic tests in the evaluation of GERD.

Esophageal 24 hr pH monitoring*
Esophagram
Upper gastrointestinal series
Gastric emptying study
Esophagogastroduodenoscopy (EGD)
Esophageal impedance
Esophageal manometry

\* Gold standard.

TABLE 3: Common indications for antireflux procedures.

Failed or refractive medical management
Severe pulmonary disease associated with GERD*
GERD in neurologically impaired children
Esophageal stricture, recurrent esophagitis*, Barrett's esophagus
Feeding disorders associated with reflux*
Failure to thrive*

\* Most common indications for antireflux surgery in the US [10].

is even more important in those patients experiencing GERD symptoms.

Surgical management of GERD typically becomes necessary in presence of GER complications and/or failed medical therapy. It is considered for the patient with esophagitis, stricture, pulmonary symptoms such as asthma and recurrent pneumonia, and finally those with failure or inadequate response to medical therapy associated with neurologic handicaps [18, 19]. See Table 3 for a list of common indications for surgical management. Antireflux procedures are usually performed to eradicate the reflux of gastric contents into the esophagus which should control GERD related symptoms, prevent complications, and permit adequate caloric intake to achieve growth [20]. This is achieved by reestablishing the gastroesophageal barrier through creation of a partial or complete valve mechanism at the gastroesophageal junction (fundoplication) [7]. Over the years, laparoscopic antireflux procedures (first reported in children in 1993) have replaced the open approach to become the primary surgical approach for the treatment of GERD [11, 21].

**4.1. Fundoplication.** Fundoplication provides definitive treatment for GERD and is highly effective in most circumstances. The fundus of the stomach can be wrapped around the distal esophagus either 360 degrees (i.e., Nissen fundoplication) or to lesser degrees (i.e., Thal or Toupet fundoplication). Initially described in 1954 by Rudolph Nissen, the Nissen fundoplication has evolved to become the standard operation for the surgical treatment of GERD in children and adults [17]. Nissen described the procedure as a 360 degree gastric fundoplication around the distal esophagus for a distance of 4-5 centimeters. This provided solid control of reflux but was associated with numerous side effects that encouraged modifications to the procedure. These changes included using

TABLE 4: Essential steps to the laparoscopic Nissen. See Figures 1–3 for images of these steps.

Gastroesophageal junction (GEJ) mobilization with identification of main vagi trunks
Hiatal dissection and creation of retroesophageal window
Division of short gastric vessels/gastrosplenic ligament
Crural approximation
Creation of a 360° wrap with a bougie in place

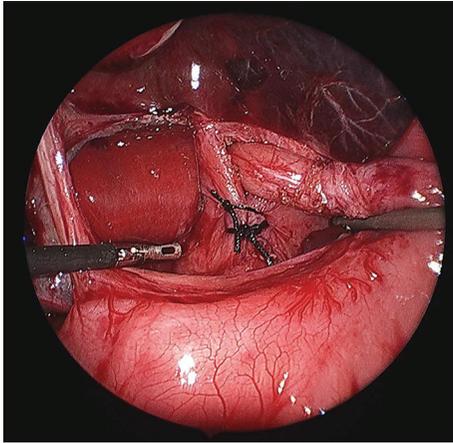


FIGURE 1: Laparoscopic Nissen fundoplication technique. Esophageal mobilization with creation of a retroesophageal window and crural approximation (sutures).

only the gastric fundus to surround the esophagus and limiting the length of the fundoplication to 1 to 2 centimeters [22]. The essential steps to performing both an open and laparoscopic fundoplication can be found in Table 4. Figures 1, 2, and 3 also highlight key steps of the laparoscopic fundoplication.

**4.2. Partial Fundoplication.** Partial fundoplication procedures involve wrapping the distal esophagus to a lesser degree than required in the Nissen procedure (e.g., 270 degrees). Partial wraps are often performed in those patients with esophageal motility disorders to prevent dysphagia that may result from a complete fundoplication. The most commonly performed partial fundoplications are Toupet (posterior) and Thal (anterior). The steps of the Toupet procedure are similar to the Nissen; however, once the fundus is mobilized posteriorly around the esophagus, the edges of the fundus are sutured to the right and left sides of the distal esophagus which ensures that the wrap only partially encircles the esophagus (posteriorly). A Thal is performed by approximating the hiatus posterior to the esophagus and then the fundus is sutured anteriorly with fixation to the esophagus and the diaphragm (anteriorly).

**4.3. Nissen versus Partial Fundoplication.** Currently, there are four large retrospective studies in the literature that compare

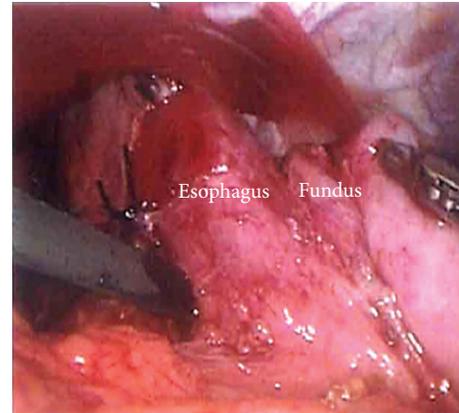


FIGURE 2: Laparoscopic Nissen fundoplication technique. Creation of the fundoplication “wrap” by passing the fundus of the stomach behind the esophagus (through the retroesophageal window). This is called the “shoe shine maneuver.”

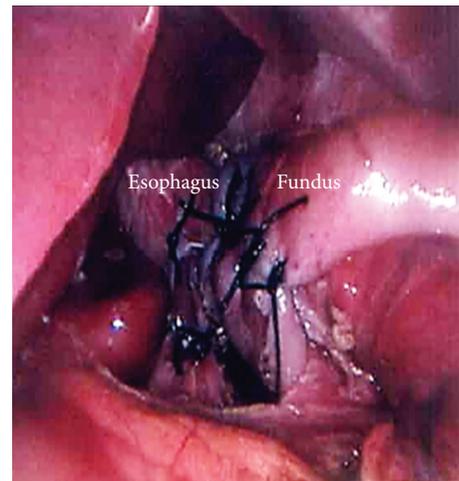


FIGURE 3: Laparoscopic Nissen fundoplication technique. Completed 360° fundoplication.

the different laparoscopic fundoplication techniques in children. In 2001, Esposito et al. [23] showed that laparoscopic fundoplication was feasible even in pediatric patients less than one year of age. In 2006 Esposito et al. then observed no statistical significance in outcome between laparoscopic Nissen, Toupet, and Thal procedures in neurologically normal children in the hands of experienced pediatric surgeons [24] (Table 5). Similarly, Chung and Georgeson [12] and Steyaert et al. [13] reported that Nissen and Toupet procedures were comparable with regard to reflux control. Among the four studies, the reoperation rate ranged between 2.1% and 11.1%, with the highest incidence reported by Esposito et al. [23] in 36 infants [12, 13, 23, 24]. Kubiak et al. [15] published the first prospective randomized trial seeking to compare the long-term outcomes and control of symptoms after Nissen and Thal fundoplications in children. In this study, the Nissen fundoplication had a significantly lower recurrence rate than the Thal (5.9% versus 15.9%) in patients with

TABLE 5: Outcomes in antireflux surgery. Ranges based on retrospective reviews by Mattioli et al. [11], Chung and Georgeson [12], Steyaert et al. [13], and Subramaniam and Dickson [14] and randomized prospective study by Kubiak et al. [15]. Those categories with only one percentage value represent the only study that individually looked at a particular outcome category for either Nissen, Toupet, or Thal.

	Dysphagia	Postoperative complications	Recurrence rates	Repeat surgical intervention
Nissen	4% to 24%	4% to 22%	3% to 46%	2% to 14%
Toupet	2%	3% to 8%	1% to 25%	~2%–11%
Thal	2% to 22%	3%	6%–20%	10%–14%

underlying neurological disorders. There was no significant difference between the fundoplications in normal children. In terms of control of symptoms, the incidence of postoperative dysphagia was similar in both groups, but significantly more patients in the Nissen group required intervention for severe dysphagia (11.8% versus 2.4%). In those patients who had a recurrence of moderate symptoms, there was no significant difference in the need to restart antireflux medication between both groups.

**4.4. Learning Curves for Laparoscopic Fundoplication.** As with any surgical technique, a period of learning is expected to master approach, technique, and avoid complications. With respect to antireflux surgery (complete and partial fundoplication), the laparoscopic approach requires the need for intracorporeal suturing and specific dissection and mobilization techniques that can be challenging to even the most experienced surgeon.

There are both adult and pediatric studies that address the learning curves associated with laparoscopic surgery. Watson et al. [25] reported an institutional learning curve of 50 procedures and individual learning curves of 20 operations from an initial experience of 280 laparoscopic antireflux procedures in adults. They also noted that the adverse effects of the learning curve could be avoided if new surgeons performed their initial cases under the direct supervision of an experienced surgeon.

In children, Meehan and Georgeson [26] looked at the learning curve in their first 160 cases of laparoscopic fundoplications and suggested a learning curve in terms of conversion to open and operative times between 20 and 25 cases. In his series of 220 procedures, Rothenberg [27] also reported an estimated learning curve for laparoscopic Nissen fundoplication to be between 20 and 50 cases.

As this learning period is to be expected, the presence/consultation of a senior surgeon during this period may mitigate longer operative times and increased risk of surgical complications. It is also important to note that the surgeon's learning curve extends as technique improves and more complicated patients are referred for operation [28].

**4.5. Fundoplication Plus Gastrostomy.** Though a large number of patients who require a fundoplication also receive a gastrostomy, children with intact swallowing or those who were not dependent on gastrostomy or tube feeding before antireflux surgery are candidates for fundoplication alone [7]. In those children with a preexisting gastrostomy, the tube can interfere with dissection of the hiatus or performance of the

wrap and create too much tension on the fundus to perform an adequate fundoplication. Therefore, if leaving the old gastrostomy tube in place will compromise the performance of the fundoplication, the authors prefer to take down the old site, close with suture repair, and replace it at the end of the procedure.

**4.6. Fundoplication Plus Pyloroplasty.** Delayed gastric emptying is associated with a significant number of patients with GERD and has also been reported in the postoperative period [7]. This has brought into question whether a pyloroplasty should be performed at the time of fundoplication. The outcomes of children who have undergone Nissen fundoplication with pyloroplasty are similar to those who have been treated without pyloroplasty in terms of recurrence of symptoms, reoperation, and readmission [29]. However, short-term postoperative complications have been reported to be higher when pyloroplasty was added to the antireflux procedure [29]. Lastly, improved gastric emptying after fundoplication as documented by preoperative and postoperative gastric emptying scans in both adults and children has led to the common practice for surgeons to perform fundoplication without pyloroplasty [30, 31].

**4.7. Gastrostomy.** The challenges that result from failed fundoplication have led to the implementation of alternative surgical management strategies for GERD [17]. Many children who require gastrostomy placement often have coexistent GER [32]. This is particularly true in neurologically impaired children. In the past, those requiring a gastrostomy tube would also receive an antireflux procedure at the time of tube placement. Neurologically impaired children have been shown to have a poorer prognosis following antireflux surgery compared to neurologically normal children [33]. Consequently, several studies sought to challenge the notion that an antireflux surgery should still be performed irrespective of GER symptom resolution with gastrostomy tube placement. A retrospective analysis by Wilson et al. [32] in 2006 reported that symptoms of GERD were alleviated in 68% of children with gastrostomy alone. Fourteen percent of those who had persistent GER symptoms responded with the addition of antireflux medications and only 7% of the included patients eventually required an antireflux procedure. While the mechanism for symptom improvement is unclear, this study does suggest that it may be a viable surgical alternative, particularly in neurologically impaired children that may have other coexisting medical conditions

that increase preoperative surgical risk. This issue is still controversial, however, as a retrospective analysis by Srivastava et al. in 2009 revealed that reflux-related hospital admissions for neurologically impaired children who underwent Nissen fundoplication were reduced compared to hospital admissions before-fundoplication [34].

**4.8. Gastrojejunal Feeding.** Of all the surgical management procedures, the least invasive is the placement of a nasojejunal or gastrojejunal feeding tube. This allows the stomach to be bypassed, preventing food contents from entering the esophagus, and often results in symptom improvement. This technique is limited, however, as a long-term management strategy. Patient comfort, tube dislodgement, inability to bolus feed, the need for lifelong antireflux medications, and rarely enteroenteric intussusceptions are often cited as disadvantages to this management option. Some literature suggests that this option is best reserved for those neurologically impaired children with increased operative risk [35].

**4.9. Total Esophagogastric Dissociation.** Originally described by Bianchi in 1997, total esophagogastric dissociation emerged as a surgical option for those who have repeatedly failed attempts at fundoplication or have severe neurologic impairment [36]. This procedure permanently eliminates GERD by transecting the esophagus from the stomach and creating an esophagojejunal (EJ) anastomosis. The biliopancreatic limb is then anastomosed to the jejunal loop approximately 30 cm distal to the EJ anastomosis in order to drain the gastric contents. This procedure was recently shown to be feasible laparoscopically in children [37]. In addition, gastric feedings may still be utilized via a gastrostomy tube in the remnant stomach without the risk of reflux.

**4.10. Endoscopic Approaches.** During the past few years, a number of endoscopic procedures aimed at improvement of the barrier function of the lower esophageal sphincter (LES) have emerged. In general, these endoscopic techniques use two different approaches to reduce reflux and improve the gastroesophageal barrier function. In one approach the GE junction can be tightened by the endoscopic creation of plications and in another radiofrequency energy is delivered to the lower esophagus and cardia to obtain collagen remodeling and augment LES pressure.

Endoluminal gastroplication involves the endoscopic creation of multiple folds or plicae in the stomach below the LES. In 2004, Thomson et al. [38] reported their initial experience performing this procedure in children. In 2008, they reported their medium-term outcome which showed 88% of patients symptom free with no need for antireflux medications at 1 year, 56% at 3 years and a rate of symptom recurrence requiring reoperation of 25% at 3 years [39]. There are no data regarding the long-term outcomes of gastroplication in children.

The next endoscopic procedure that has been described in children is the Stretta procedure. In this procedure, radiofrequency energy is delivered in multiple levels around the GE junction (approximately 2-3 cm). The intent is to

create a high pressure zone that reduces reflux through scarring of the lower esophagus. This scarring not only creates a high pressure zone but it also causes a decrease in the number of transient LES relaxations due to disruption of adjacent vagal afferent fibers [40]. Studies in adults show questionable improvement in GERD symptoms, patient satisfaction, quality of life, and need for medication sustained over 4 years of followup, and the use of Stretta in children is based on type III evidence [9, 17, 41]. At this point based on the limited data and lack of long-term outcomes, both the Stretta and endoluminal gastroplication techniques are included for historical perspective and context. They cannot be recommended as surgical options for the treatment of GERD in children.

## 5. Surgical Complications

Antireflux surgery complications can be divided into short and long-term events. Short-term will describe intraoperative and initial postoperative period complications. Long-term complications will refer to those complications developing several months to years after the initial procedure.

**5.1. Intraoperative Complications.** Bleeding, esophageal and gastric perforation (all repaired laparoscopically), vagus nerve injury, bowel injury, and pneumothorax have all been reported as intraoperative complications of laparoscopic antireflux surgery. The reported rate of these complications is between 0.5% and 11% [42-44].

**5.2. Postoperative Complications.** The challenge of any antireflux procedure is to reestablish the gastroesophageal barrier and eradicate symptoms of reflux without inducing dysphagia and hyperflatulence, symptoms that often characterize wraps that have been too tightly placed. Complications of surgery in the initial postoperative period are uncommon but include dysphagia and gas bloat. Dysphagia rates are reported to range from <1% to 23% [15, 42]. For dysphagia, the child is kept on liquid and semisolid foods until the dysphagia resolves which usually occurs by 3 weeks following the operation. As mentioned earlier in this paper, while dysphagia rates have been reported to be similar across all fundoplication types [24], the Nissen fundoplication has been shown to have a higher rate of severe dysphagia that required intervention than those patients who received a Thal fundoplication [15].

**5.3. Long-Term Complications.** Failed laparoscopic fundoplication defined as abnormal pH studies with symptoms has been shown to occur in 2% of neurologically normal and in up to 12% of neurologically impaired children [45]. Recurrence or persistence of reflux symptoms (i.e., heartburn and regurgitation) and postoperative persistent dysphagia are the most common indicators for failure of Nissen fundoplication. See Table 6 for common causes of fundoplication failure and Figure 4 for radiographic imaging which shows a slipped fundoplication with intrathoracic herniation.

When patient symptoms persist, a "redo" fundoplication, whether open or laparoscopic, has been shown to be a safe

TABLE 6: Common causes of fundoplication failure described by Hunter et al. [16].

- 
- (1) Disruption of wrap
  - (2) Wrap slippage
  - (3) Sliding hernia with intact wrap
  - (4) Overly tight or long fundoplication
  - (5) Intrathoracic herniation of wrap (paraesophageal hernia)
  - (6) Twisted wrap
- 



FIGURE 4: Upper gastrointestinal series. This imaging study reveals a slipped wrap with intrathoracic herniation (arrow).

option in the hands of an experienced pediatric surgeon with a 2-year failure rate of 6% [46]. While a redo fundoplication is feasible, it should be noted that successful repair can be technically challenging and entails extensive adhesiolysis, esophageal mobilization, crural repair, and wrap reformation [43].

## 6. Postoperative Care

The postoperative care of for an uncomplicated patient involves advancement of diet to liquids on the first postoperative day. This includes those patients with a gastrostomy. Once the patients have tolerated liquids, they can be advanced to a pureed diet which they are to remain on for at least 3 weeks. Outpatient care should include documentation of weight gain, food tolerance, and resolution of symptoms. Routine postoperative imaging such as an upper GI series is only indicated in the case of recurrence of symptoms or evidence of recurrent GERD.

## 7. Summary

Gastroesophageal reflux is a common occurrence in the pediatric population. The majority of cases represent physiologic GER and as the LES matures and a solid diet is introduced,

many of these patients (>65%) experience spontaneous resolution of their symptoms by two years of age. Those who continue to have symptoms and develop complications such as failure to thrive, secondary respiratory disease and others are classified as having GERD. Goals of treatment include the resolution of symptoms and prevention of complications. Treatment options to achieve these goals include dietary or behavioral modifications, pharmacologic intervention, and surgical therapy. Overall, management of GERD in both adults and children is based on disease severity, the degree of symptoms, and presence or absence of complications of GER determined by diagnostic evaluation. The laparoscopic Nissen fundoplication is the standard operation for the surgical treatment of GERD. Partial fundoplications can also be performed, particularly in cases of underlying esophageal motility disorders, but it has been shown in some studies to have a higher recurrence rate than the Nissen fundoplication. Other techniques include gastrojejunal feeding, gastrostomy, and total esophagogastric dissociation and have promising early results in children. Uncomplicated postoperative care for fundoplications include early advancement of diet to liquids then pureed and outpatient documentation of resolution of symptoms. Complications of surgery include both short term (intraoperative, postop dysphagia, and hyperflatulence) and long term (failed fundoplication). The learning curve for antireflux surgery is approximated to be between 20 and 50 cases but continues to extend as the surgeon is referred more complicated cases. In the case of failed fundoplication, a “redo” procedure is safe and appropriate in the hands of an experienced surgeon.

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## Clinical Study

# Duodenal Tube Feeding: An Alternative Approach for Effectively Promoting Weight Gain in Children with Gastroesophageal Reflux and Congenital Heart Disease

Seiko Kuwata,<sup>1</sup> Yoichi Iwamoto,<sup>1</sup> Hirotaka Ishido,<sup>1</sup>  
Mio Taketadu,<sup>1</sup> Masanori Tamura,<sup>1</sup> and Hideaki Senzaki<sup>1,2</sup>

<sup>1</sup> Department of Pediatrics and Pediatric Cardiology, Saitama Medical University, Saitama, Japan

<sup>2</sup> Department of Pediatric Cardiology, Saitama Medical Center, Saitama Medical University, Staff Office Building 101, 1985 Kamoda, Kawagoe, Saitama 350-1981, Japan

Correspondence should be addressed to Hideaki Senzaki; [hsenzaki@saitama-med.ac.jp](mailto:hsenzaki@saitama-med.ac.jp)

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We tested whether duodenal tube feeding effectively improves the clinical symptoms and body weight gain in children with congenital heart disease (CHD) and gastroesophageal reflux (GER). In the retrospective analysis of 17 consecutive children with CHD who were treated with duodenal tube feeding for symptomatic GER, we found that clinical symptoms of persistent emesis or respiratory wheezing after feeding disappeared with duodenal tube feeding in all patients. Duodenal tube feeding facilitated a stable nutritional supply, resulting in marked improvement of weight gain from 6 to 21 g/day ( $P < .0001$ ). In a patient with trisomy 21 and persistent pulmonary hypertension after the closure of a ventricular septal defect, duodenal tube feeding ameliorated pulmonary hypertension, as evidenced by the improvement of the pressure gradient of tricuspid regurgitation from 77 to 41 mm Hg. In 14 of the 17 patients, the duodenal tube was successfully removed, with the spontaneous improvement of GER (median duration of duodenal tube feeding: 7 months). In conclusion, duodenal tube feeding improves the weight gain of infants with GER who need treatment for CHD-associated heart failure. It also allows for the improvement of pulmonary hypertension.

## 1. Introduction

Body weight gain is important for the successful treatment for infants with heart failure associated with congenital heart disease (CHD). Gastroesophageal reflux (GER) is known to be relatively common in this condition and is occasionally an important cause of growth failure in affected patients [1]. It can also cause aspiration pneumonia and pulmonary arterial hypertension, thus potentially complicating the clinical course of heart failure [2]. Medical therapy with gastric acidity inhibitors, including histamine-2 receptor antagonists and proton pump inhibitors, is the first line of treatment; however, it is not always effective [3–6]. In such cases, antireflux surgical procedures are selected [7–10]. Another treatment option may be the administration of duodenal tube feeding, which is less invasive than surgical procedures and thus may be beneficial for this particular group of patients for

whom invasive interventions with general anesthesia carry a risk for worsening heart failure. However, little information is available about the efficacy of duodenal tube feeding for infants with GER and heart failure associated with CHD. In this study, we reviewed our experience of duodenal tube feeding performed in 17 children with CHD-associated heart failure, focusing on its efficacy in terms of body weight gain. We also evaluated its effect on GER-induced pulmonary hypertension.

## 2. Methods

Seventeen consecutive infants and children with preoperative ( $n = 3$ ) and postoperative ( $n = 14$ ) CHD and heart failure who were treated with duodenal tube feeding were analyzed. These patients had episodes of frequent vomiting

TABLE 1: Patients' Characteristics.

Birth weight, g	2607 ± 321
Age at the time of diagnosis, months	4.7 ± 0.5
Body weight at the time of GER diagnosis	3667 ± 420
Types of congenital heart defects ( <i>n</i> )	
Tetralogy of Fallot	4 (1)
Single ventricle	2 (1)
Atrioventricular septal defect	2 (1)
Coarctation of the aorta	1
Coarctation of the aorta with ventricular septal defect	1
Transposition of the great arteries	1
Double outlet right ventricle	2
Ventricular septal defect	1
The Ebstein anomaly	1
Patent ductus arteriosus	1
Other abnormalities ( <i>n</i> )	
Trisomy 21	8 (2)
Trisomy 18	1
22q1-	2
Asplenia syndrome	2 (1)

Numbers in parentheses indicate postoperative patients.

and/or wheezing after oral or tube feeding and therefore were suspected of having GER. They underwent gastrography, which showed a reflux of contrast medium from the stomach to the esophagus beyond the halfway point between these organs. After gastrography, a weighted duodenal tube (5 Fr) was inserted under fluoroscopic guidance using a guidewire within a tube to facilitate manipulation of the tube that was then advanced beyond the descending portion of the duodenum. The appropriate position of the tube was finally confirmed by injecting a small amount of contrast medium through the tube, which showed the jejunum directly. A gastric tube is routinely placed for medication but not for gastric acid drainage. Because our patients had no gastrointestinal tract obstruction, gastric tube drainage was not performed in order to avoid potential electrolyte disturbance. Medication for reducing acid levels was continued only for severe GER patients who showed a reflux of contrast medium up to the pharynx.

We compared the body weight gain averaged for 14 to 21 days before and after duodenal tube feeding in each patient. In 1 patient (trisomy 21) who showed persistent pulmonary hypertension after the closure of a ventricular septal defect, changes in the severity of pulmonary hypertension were assessed by measuring the Doppler flow velocity of tricuspid regurgitation (TR).

### 3. Results

Table 1 summarizes the characteristics of the studied patients. Of note, 13 patients had underlying conditions of chromosomal abnormalities (*n* = 10) or anomaly syndromes

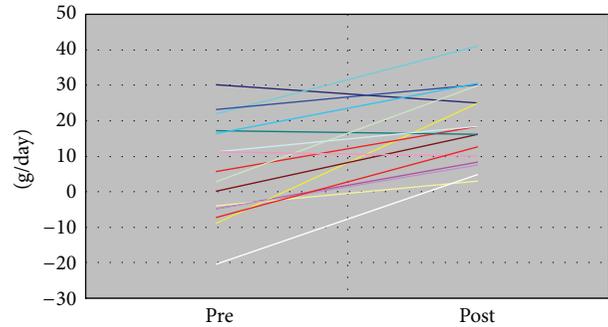


FIGURE 1: Changes in body weight gain per day before and after duodenal tube feeding.

(*n* = 3). The patients' age at the time of the initiation of duodenal tube feeding ranged from 0 to 16 months, with a median of 2 months. No adverse events occurred during the insertion of the duodenal tube. In all patients, clinical symptoms of persistent emesis or respiratory wheezing after feeding disappeared after duodenal tube feeding. Duodenal tube feeding facilitated a stable nutritional supply, resulting in marked improvement of weight gain from 6 to 21 g/day ( $P < .0001$ , Figure 1). In the patient with trisomy 21 and persistent pulmonary hypertension after the closure of a ventricular septal defect, duodenal tube feeding ameliorated the pulmonary hypertension, as evidenced by the improved pressure gradient of TR from 77 to 41 mm Hg.

In 14 of the 17 patients, the duodenal tube was successfully removed, with the spontaneous improvement of GER. The median duration of duodenal tube feeding was 7 months, ranging from 4 to 10 months. One patient who had single ventricular physiology complicated with asplenia syndrome underwent laparoscopic fundoplication after the initial cardiac surgery (the Blalock-Taussig shunt). In this particular patient, the procedure of fundoplication was difficult because of the unusual anatomical relation between the heart and the stomach, and the patient developed hypotension and cyanosis during the procedure. Another patient died of severe heart failure after cardiac surgery for the Ebstein anomaly. The remaining patient had trisomy 18 and continued duodenal tube feeding, considering the risk for both general anesthesia and antireflux surgery.

Tube-related complications associated with duodenal tube feeding included accidental removal, obstruction, or damage; in most of the patients, these complications necessitated the replacement of the tube before the scheduled 3-month replacement. In addition, enterocolitis due to multiresistant *Staphylococcus aureus* (MRSA) was observed in 1 patient during the study period.

### 4. Discussion

To the best of our knowledge, our study is the first to demonstrate that duodenal tube feeding is effective in promoting weight gain in infants and children with CHD and GER.

In general, pharmacologic therapy with gastric acidity inhibitors, including histamine-2 receptor antagonists

and proton pump inhibitors, together with maintaining an upright posture during feeding and the administration of thickened feedings, is the mainstay of GER treatment [3–6]. However, such medical therapy often fails to resolve the symptoms of GER in children [4–6]. In a particular group of infants with CHD, Weesner and Rosenthal [11] also reported very low success rates of medical therapy in resolving the infants' respiratory symptoms. In addition, the use of gastric acidity inhibitors was reported to be associated with an increased risk of acute gastroenteritis and community-acquired pneumonia in a multicenter, prospective study of children with GER [6].

In contrast, antireflux surgery for GER (i.e., the Nissen fundoplication) has been generally shown to result in a substantial improvement of reflux and the alleviation of its consequences in children without CHD [7–10]. Several studies have also reported that laparoscopic procedures can be safely performed even in infants with CHD, with careful monitoring of arterial carbon dioxide levels during insufflation [12, 13]. In addition, a recent study by Cribbs et al. [2] showed that the surgical repair of GER in their population of infants and children with severe CHD was safely performed and effectively promoted weight gain. However, they also reported 1 death among 112 procedures and 3 potentially lethal complications in the early postoperative period. These data evidence that pediatric cardiac anesthesia providers are essential for the safe performance of antireflux procedures in this population, with postoperative care administered in a dedicated cardiac intensive care unit, as suggested by the authors. Our patient with asplenia syndrome who underwent laparoscopic fundoplication indeed experienced unexpected hemodynamic instability during the procedure even under the care of our pediatric anesthesiologists.

Compared with surgical procedures, insertion of a duodenal tube does not require general anesthesia or postoperative intensive care, which would be a major advantage of this approach. With the low procedural risk, duodenal tube feeding consistently ameliorated GER-related symptoms and resulted in a dramatic improvement of weight gain. In addition to being less invasive, duodenal tube feeding may have another merit in that it can be terminated upon the subsequent resolution of GER. There has been no clear information about whether GER associated with CHD can improve over time. In this sense, our study clearly demonstrated that most of our studied population outgrew reflux, and the duodenal tube was successfully removed within 10 months after the initiation. Because the timing of the follow-up gastrography to check for GER status was arbitrary in our patients, the periods of duodenal tube feeding could have been even shorter than the actual duration of 10 months. In the least, duodenal tube feeding can avoid antireflux surgery in symptomatic GER patients with CHD. Duodenal tube feeding may also be useful as a bridge to fundoplication particularly in preoperative CHD patients, as in our asplenia patient who underwent fundoplication after the temporal administration of duodenal tube feeding. Fundoplication may be more safely performed under stable hemodynamic conditions established after cardiac surgery.

Our study also demonstrated the improvement of pulmonary hypertension by duodenal tube feeding in a trisomy 21 patient after a corrective surgery for CHD. This is consistent with our previous report on a Down syndrome infant without structural cardiac anomaly [14]. Down syndrome is known to be associated with an increased prevalence of GER. The syndrome is also known to pose a high risk for postoperative persistent pulmonary hypertension. The present case, together with our previous one, highlights the importance of a high index of suspicion for GER as a curable cause of pulmonary artery hypertension in this syndrome.

Finally, tube dislodgement, migration, diarrhea, and enterocolitis are known to occur occasionally with duodenal tube feeding. In fact, we experienced tube-related complications such as accidental removal, obstruction, and damage that necessitated unscheduled tube replacement in most patients. Education and training of both family and medical staff are essential for minimizing these events. In addition to these tube-related complications, 1 patient in our study experienced MRSA enterocolitis during duodenal tube feeding. Although a cause-effect relationship between duodenal tube feeding and the occurrence of MRSA enterocolitis was not clear, intestinal tract infection is a known potential important complication associated with duodenal tube feeding that may occur due to reduced protective effects of gastric acid. This fact also should be kept in mind during the application of duodenal tube feeding.

## 5. Conclusions

Duodenal tube feeding is a less invasive method for promoting weight gain in symptomatic children with GER associated with CHD. It can be terminated upon the spontaneous resolution of GER with the patient's growth. Thus, duodenal tube feeding should be considered a useful alternative to surgery in CHD patients with GER.

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## Research Article

# Changes in Ghrelin-Related Factors in Gastroesophageal Reflux Disease in Rats

Miwa Nahata,<sup>1</sup> Yayoi Saegusa,<sup>1</sup> Yumi Harada,<sup>1</sup> Naoko Tsuchiya,<sup>1</sup>  
Tomohisa Hattori,<sup>1</sup> and Hiroshi Takeda<sup>2,3</sup>

<sup>1</sup> Tsumura & Co., Tsumura Research Laboratories, 3586 Yoshiwara, Ami-machi, Inashiki-gun, Ibaraki 300-1192, Japan

<sup>2</sup> Department of Gastroenterology and Hematology, Hokkaido University Graduate School of Medicine, N15 W7 Kita-ku, Sapporo, Hokkaido 060-8638, Japan

<sup>3</sup> Department of Pathophysiology and Therapeutics, Division of Pharmasciences, Faculty of Pharmaceutical Sciences, Hokkaido University, N12 W6 Kita-ku, Sapporo, Hokkaido 060-0812, Japan

Correspondence should be addressed to Tomohisa Hattori; [hattori\\_tomohisa@mail.tsumura.co.jp](mailto:hattori_tomohisa@mail.tsumura.co.jp)

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To examine gastrointestinal hormone profiles and functional changes in gastroesophageal reflux disease (GERD), blood levels of the orexigenic hormone ghrelin were measured in rats with experimentally induced GERD. During the experiment, plasma acyl ghrelin levels in GERD rats were higher than those in sham-operated rats, although food intake was reduced in GERD rats. Although plasma levels of the appetite-suppressing hormone leptin were significantly decreased in GERD rats, no changes were observed in cholecystokinin levels. Repeated administration of rat ghrelin to GERD rats had no effect on the reduction in body weight or food intake. Therefore, these results suggest that aberrantly increased secretion of peripheral ghrelin and decreased ghrelin responsiveness may occur in GERD rats. Neuropeptide Y and agouti-related peptide mRNA expression in the hypothalamus of GERD rats was significantly increased, whereas proopiomelanocortin mRNA expression was significantly decreased compared to that in sham-operated rats. However, melanin-concentrating hormone (MCH) and prepro-orexin mRNA expression in the hypothalamus of GERD rats was similar to that in sham-operated rats. These results suggest that although GERD rats have higher plasma ghrelin levels, ghrelin signaling in GERD rats may be suppressed due to reduced MCH and/or orexin synthesis in the hypothalamus.

## 1. Introduction

Gastroesophageal reflux disease (GERD) is caused when gastric acid flows back into the esophagus, resulting in erosion of the esophageal mucosal epithelium. Gastric secretion inhibitors, such as proton pump inhibitors, can alleviate GERD symptoms [1]. Moreover, gastric acid reflux into the esophagus characteristically increases after eating [2], and although GERD patients sometimes complain of nausea and a loss of appetite, the acid reflux into the esophagus that causes GERD may instead be partially due to the amount and content of food. There are various peripheral and central appetite-related hormones involved in the control of appetite and satiation; ghrelin is secreted by the stomach and stimulates appetite and gastrointestinal motility [3], whereas

cholecystokinin (CCK) and leptin, which are secreted in response to food intake, suppress appetite [4, 5]. Ghrelin is secreted by X/A-like cells found in the gastric mucosa, and it binds to the growth hormone secretagogue receptor (GHS-R) present at the end of the vagus nerve to stimulate feeding behavior by suppressing the satiety stimulus transmitted by CCK [6, 7]. In contrast, leptin is secreted by fat cells and acts directly on the hypothalamus by crossing the blood-brain barrier, thereby suppressing food intake desire caused by ghrelin [5]. Until date, changes in appetite-related hormones in GERD patients have not been sufficiently characterized. We hypothesized that the progression of GERD may be mediated by the abnormal function of appetite-related hormones. As a first step in elucidating the involvement of appetite-related hormones in GERD, we examined the profiles of

peripheral appetite-related peptides, with a focus on changes in ghrelin levels and ghrelin responsiveness.

## 2. Materials and Methods

**2.1. Animals.** Eight-week-old male Wistar rats (CLEA Japan, Tokyo, Japan) were used during the experiment. During testing, 4-5 animals were housed in a single cage and were allowed free access to food and water. Animal rooms were illuminated between 07:00 and 19:00, and temperature and humidity were maintained at constant levels. All tests were performed between 09:00 and 18:00, according to the guidelines of the Experimental Animal Ethics Committee of Tsumura.

**2.2. Chemicals.** Rat ghrelin was obtained from the Peptide Institute (Osaka, Japan) and was dissolved in 0.9% sterilized physiological saline (Otsuka Pharmaceutical, Tokyo, Japan).

**2.3. Preparation of GERD Rats.** GERD was surgically induced by Omura's method [8]. Rats deprived of food for 24 h were anesthetized with ether. The abdomen was opened using a 2 cm upper-median abdominal incision. The stomach and duodenum were exteriorized, and the boundary between the forestomach and the glandular stomach was sutured with 1-0 silk thread (Natsume Seisakusho, Tokyo, Japan). A precut 2 mm wide 18-Fr Nelaton catheter (Terumo, Tokyo, Japan) was used to cover the area proximal to the pylorus on the duodenal side, and a 5-0 nylon thread (Natsume Seisakusho, Tokyo, Japan) was used to suture and fix it to the surface of the pyloric serous membrane. The stomach and duodenum were placed back into the abdominal cavity, which was then closed. Sham-operated rats were first laparotomized to expose their stomach and duodenum for about 1 min, after which their abdominal cavities were closed. After surgery, rats were fasted for an additional 24 h (resulting in a total of 48 h). GERD-induced animals that were noted to have developed organ adhesions or abscesses or extreme weight loss or weakness were excluded from the experiment. To avoid a dramatic reduction in the sample, more GERD-induced animals were created than sham-operated rats.

**2.4. Measurement of Body Weight and Food Intake.** The rats were housed individually after GERD induction. Daily body weight was measured from the day of surgery, and daily food intake, calculated as the difference between preprandial and postprandial weight of the food, was measured from 2 days after surgery (day 2). On day 9, rats were deprived of food for 24 h and then sacrificed to perform histopathological assessment of the esophagus.

**2.5. Histopathological Assessment.** After 24 h of fasting (day 10), rats were exsanguinated via the abdominal vena cava under ether anesthesia, and the esophagus was excised. Histopathological assessment was performed as previously described [9]. The esophagus was opened with a longitudinal incision and immobilized on a rubber plate with insect pins. The entire esophagus was photographed, and each image

was imported into an image analysis software (WinROOF; Mitani Corporation, Tokyo, Japan). Sites showing esophageal mucosal erosion were identified and their total area was measured.

**2.6. Effect of Exogenous Ghrelin in GERD Rats.** During GERD-inducing surgery, rats were anesthetized by intraperitoneal injection of pentobarbital sodium (Kyoritsu Seiyaku, Tokyo, Japan), and a catheter filled with heparin in physiological saline was fixed to the jugular vein. The catheter was passed subcutaneously and pulled out from the back, which was then covered with a metal spring to prevent it from being bitten. After surgery, rats were housed individually and fasted for an additional 24 h. From the next day, rat ghrelin (3 nmol/rat) was administered to the rats once daily through the jugular vein for 6 days. The control group of GERD and sham-operated rats were administered saline. Daily body weight was measured from the day of surgery and daily food intake from day 2 after surgery.

**2.7. Determination of Plasma Ghrelin and Appetite-Related Hormones.** Blood was collected from the abdominal vena cava under ether anesthesia on days 3, 7, and 10 after surgery. Plasma samples were obtained as previously reported [10]. In brief, blood was collected in a tube containing EDTA-2Na (Dojindo Laboratories, Kumamoto, Japan) and aprotinin (Wako Pure Chemical Industries, Osaka, Japan). Blood samples were immediately centrifuged at 4°C, and the supernatant was acidified with 1 mol/L HCl (1/10 volume). Plasma was stored at -80°C until measurement. Plasma ghrelin levels were measured using the Active Ghrelin ELISA Kit and Desacyl Ghrelin ELISA Kit (Mitsubishi Chemical Medience, Tokyo, Japan). Plasma CCK levels were measured with the CCK EIA Kit (Phoenix Pharmaceuticals, Burlingame, CA, USA) using nonacidified plasma samples obtained in the same manner. Plasma leptin levels were measured using the Bio-Plex suspension array system (BioRad Laboratories, Hercules, CA, USA) with the Bio-Plex Pro Rat Diabetes assay panel (BioRad Laboratories).

**2.8. RNA Extraction, Reverse Transcription, and Real-Time Polymerase Chain Reaction.** After collection of blood samples, the stomach and hypothalamus were immediately excised on days 3, 7, and 10 and stored at -80°C until measurement. The tissue was homogenized and total RNA was extracted using the RNeasy Universal Tissue Kit (Qiagen, Valencia, CA, USA). Total RNA from each sample was diluted to 100 ng/ $\mu$ L, allowed to react for 5 min at 70°C, and immediately cooled on ice. An aliquot of 1  $\mu$ g of total RNA was reverse transcribed using the TaqMan Reverse Transcription Reagents (Applied Biosystems, Foster City, CA, USA) according to the manufacturer's protocol.

Quantitative polymerase chain reaction (PCR) was performed with the PRISM 7900HT Sequence Detection System (Applied Biosystems) using the TaqMan Universal PCR Master Mix (Applied Biosystems). To compensate for the differences in the amount of total RNA added to each reaction, mRNA expression was normalized to  $\beta$ -actin as an

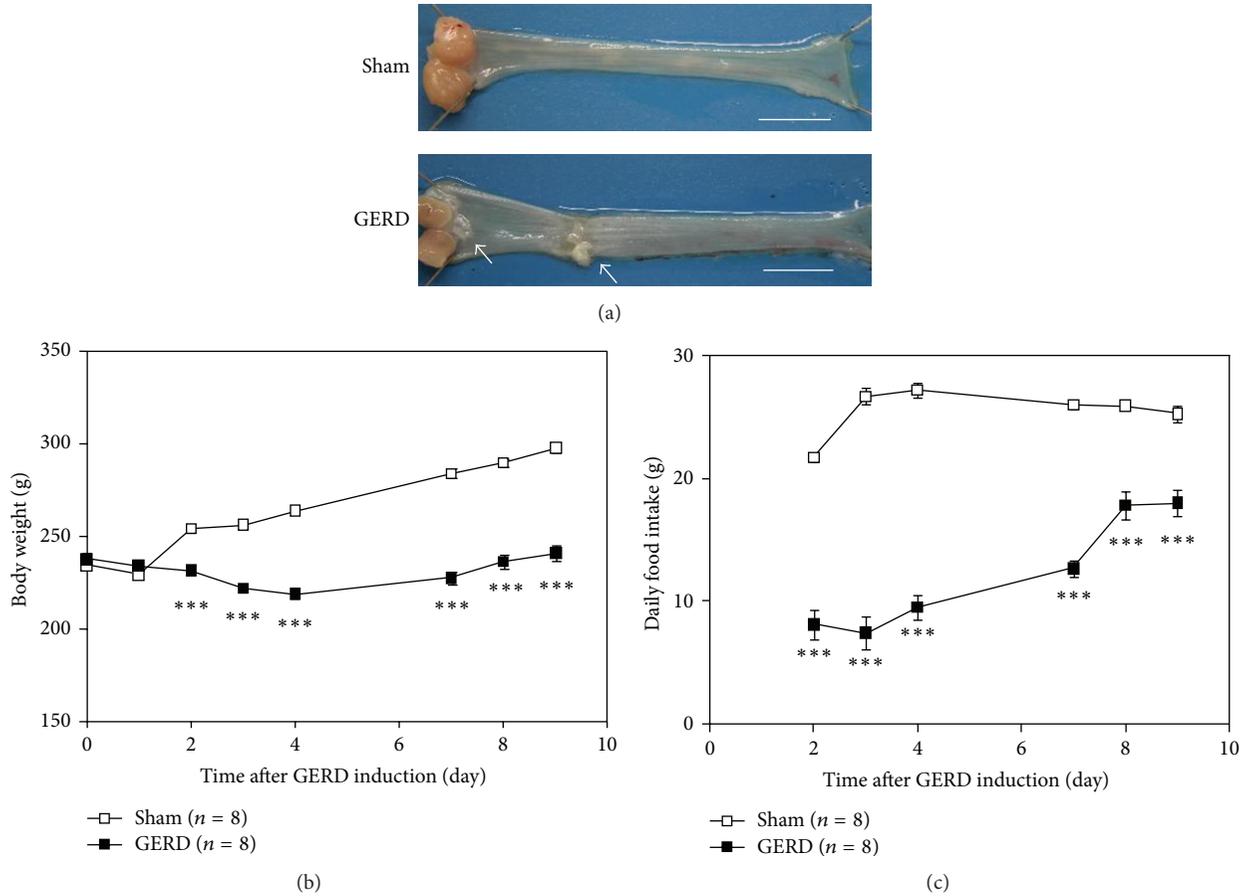


FIGURE 1: Comparison of esophageal mucosa, body weight, and food intake between sham-operated and GERD rats. (a) Esophagus on day 10 after GERD induction showed obvious erosion. Bar, 10 mm. (b) Body weight and (c) daily food intake. \*\*\* $P < 0.001$  versus sham-operated rats.

endogenous control as expressed by the  $\Delta$  threshold cycle ( $\Delta C_t$ ) value:

$$\Delta C_t = 2^{-(A - B)}, \quad (1)$$

where  $A$  is the number of cycles that reached the  $\beta$ -actin gene threshold and  $B$  is the number of cycles that reached the target gene threshold. The set of oligonucleotide primers and fluorescent probes used in TaqMan quantitative PCR was provided by Applied Biosystems: cytoplasmic  $\beta$ -actin, Rn00667869\_ml; prepro-ghrelin, Rn00572319\_ml; GHS-R, Rn00821417\_ml; membrane bound  $O$ -acyltransferase domain containing 4 (ghrelin  $O$ -acyltransferase; GOAT), Rn02079102\_sl; neuropeptide Y (NPY): Rn00561681\_ml; agouti-related protein (AgRP): Rn01431703\_gl; proopiomelanocortin (POMC): Rn00595020\_ml; promelanin-concentrating hormone (MCH): Rn00561766\_gl; and hypocretin (prepro-orexin), Rn00565995\_ml.

2.9. *Statistical Analysis.* Statistical significance was examined using Student's  $t$ -test and  $P < 0.05$  was considered statistically significant. Data were expressed as the mean  $\pm$  SEM of each group.

### 3. Results

3.1. *General Condition and Histology in GERD Rats.* Mucosal erosion was clearly observed in the esophagus of GERD rats on day 10 (Figure 1(a)). The number of erosion sites in GERD rats was  $2.5 \pm 0.4$  with a total area of  $39.7 \pm 9.8 \text{ mm}^2$ . Moreover, the body weight and food intake in these rats had significantly decreased compared with those in sham-operated rats (Figures 1(b) and 1(c)).

3.2. *Changes in Plasma Ghrelin Levels in GERD Rats.* Plasma acyl and desacyl ghrelin levels significantly increased from day 3 to day 10 (Figures 2(a) and 2(b); desacyl ghrelin levels on day 10: sham-operated,  $520.4 \pm 94.0$  versus GERD,  $832.9 \pm 92.7 \text{ fmol/mL}$ ;  $P = 0.06$ ).

3.3. *Plasma Leptin and CCK Levels in GERD Rats.* Plasma leptin levels significantly decreased on day 10 (Table 1). There were no significant differences in plasma CCK levels between GERD and sham-operated rats.

3.4. *Effect of Ghrelin Administration on Body Weight and Food Intake.* Body weight of GERD rats significantly decreased

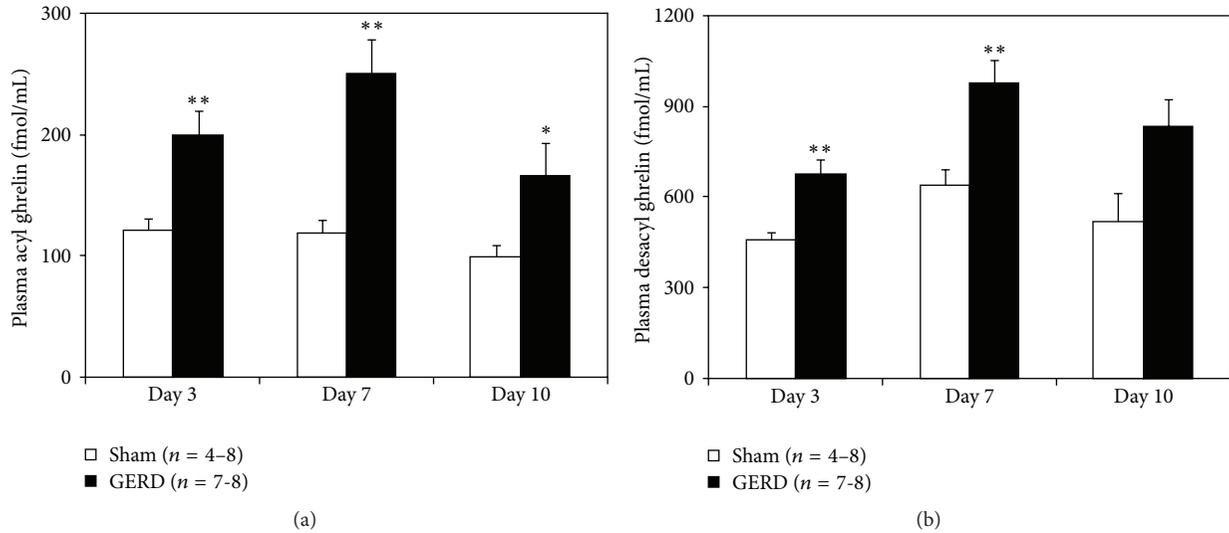


FIGURE 2: Plasma ghrelin levels in sham-operated and GERD rats on day 3, 7, and 10 after GERD induction. (a) Plasma acyl ghrelin and (b) desacyl ghrelin levels. \*, \*\* $P < 0.05, 0.01$  versus sham-operated rats on each day.

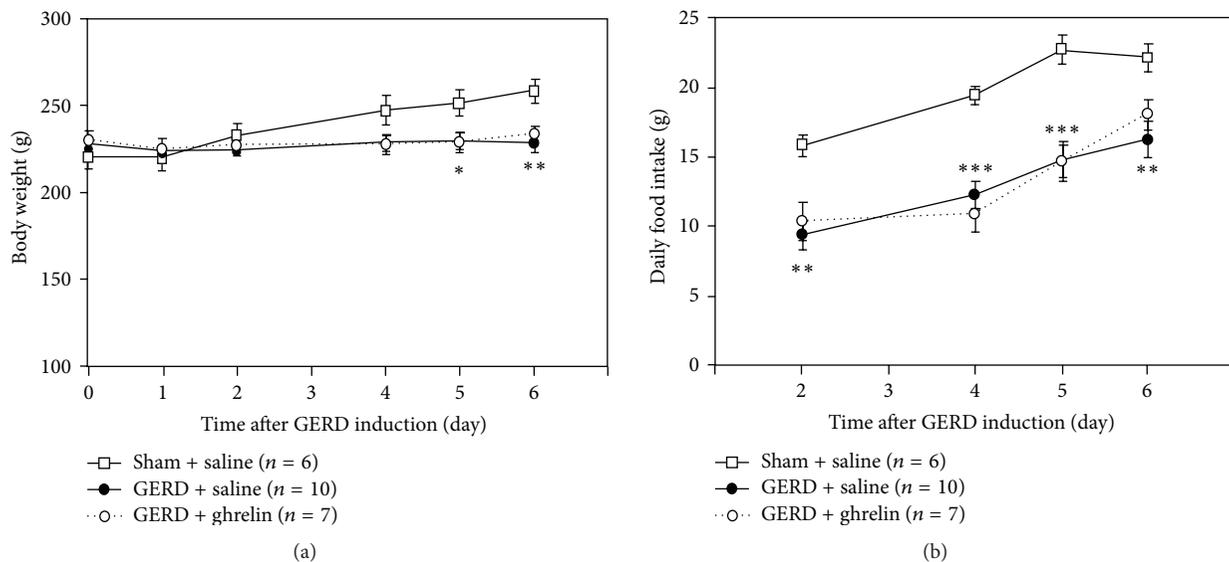


FIGURE 3: Effect of repeated administration of ghrelin to GERD rats. (a) Body weight and (b) daily food intake in sham-operated and GERD rats. Exogenous ghrelin (3 nmol/rat/day) was intravenously administered to rats once daily. Sham-operated rats and control group of GERD rats were administered saline. There were no significant differences in body weight or food intake between the saline-administered and ghrelin-administered groups in GERD rats. \*, \*\*, and \*\*\* $P < 0.05, 0.01, \text{ and } 0.001$  versus sham-operated rats on each day.

TABLE 1: Plasma leptin and cholecystinin (CCK) levels in sham-operated and GERD rats on day 10 after GERD induction.

	Sham (n = 4 or 8) (pg/mL)	GERD (n = 8) (pg/mL)
Leptin	714.6 ± 49.3	358.1 ± 78.5*
CCK	133.8 ± 8.2	112.3 ± 6.8

\* $P < 0.05$  versus sham-operated rats.

compared with that of sham-operated rats (Figure 3(a)). The repeated administration of ghrelin to GERD rats had no effect

on body weight reduction. Furthermore, there were no differences in daily food intake between GERD rats administered saline and those administered ghrelin (Figure 3(b)).

**3.5. Changes in Gastric or Hypothalamic mRNA Expression in GERD Rats.** There were no major differences in prepro-ghrelin and GHS-R mRNA expression in the stomach throughout the experiment between sham-operated and GERD rats (Figures 4(a) and 4(b)). In contrast, GOAT mRNA expression in GERD rats significantly decreased from day 7 to day 10 (Figure 4(c)). NPY mRNA expression in the

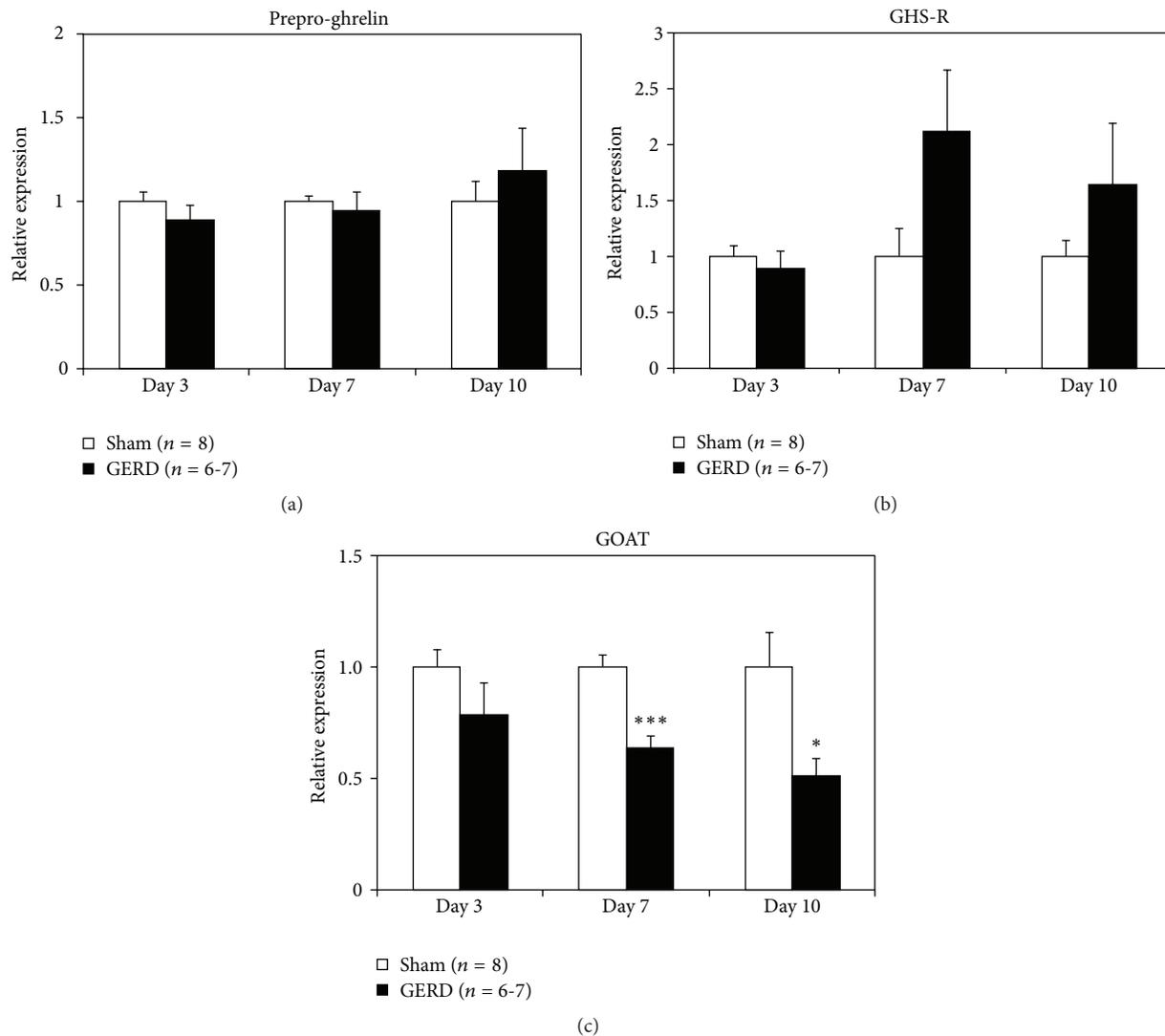


FIGURE 4: Gastric mRNA expression in sham-operated and GERD rats on days 3, 7, and 10 after GERD induction. (a) Prepro-ghrelin, (b) growth hormone secretagogue receptor (GHS-R), and (c) ghrelin O-acyltransferase (GOAT) mRNA expression. \*, \*\*\* $P < 0.05, 0.001$  versus sham-operated rats on each day.

hypothalamus of GERD rats significantly increased on day 10 (Figure 5(a)), whereas AgRP mRNA expression significantly increased from day 3 (Figure 5(b)). In contrast, a significant decrease in POMC mRNA expression was observed in GERD rats from day 7 (Figure 5(c)). In addition, MCH (Figure 5(d)) and prepro-orexin (Figure 5(e)) mRNA expression in GERD rats remained unchanged compared with that in sham-operated rats.

#### 4. Discussion

Despite the rapid increase in plasma acyl and desacyl ghrelin levels in 24-h fasted GERD rats, their food intake and body weight decreased. Repeated administration of acyl ghrelin did not suppress the reduction in food intake and body weight. Hypothalamic NPY/AgRP neuronal activity, but not MCH or orexin neurons, significantly increased. Peripheral ghrelin

signals in GERD rats were sent to the arcuate nucleus in the hypothalamus, but MCH and orexin neurons in the lateral hypothalamic area (LH) might have failed to be activated, leading to inhibition of food intake.

Ghrelin is an orexigenic hormone produced mainly in the stomach [7]. Ghrelin increases food intake and suppresses energy expenditure [3, 11]. In our previous study, we used GERD rats to demonstrate lack of responsiveness through an acute bolus administration of ghrelin (3 nmol/rat) [12]. In comparison with sham-operated rats, the growth hormone secretory effect in GERD rats intravenously administered acyl ghrelin decreased, and acute administration of acyl ghrelin did not suppress the decrease in food intake, gastric emptying, or gastric motility. Repeated administration of acyl ghrelin (3 nmol/rat/day) to GERD rats had no effect on food intake or body weight throughout the experiment in this study. We previously demonstrated that acute intravenous

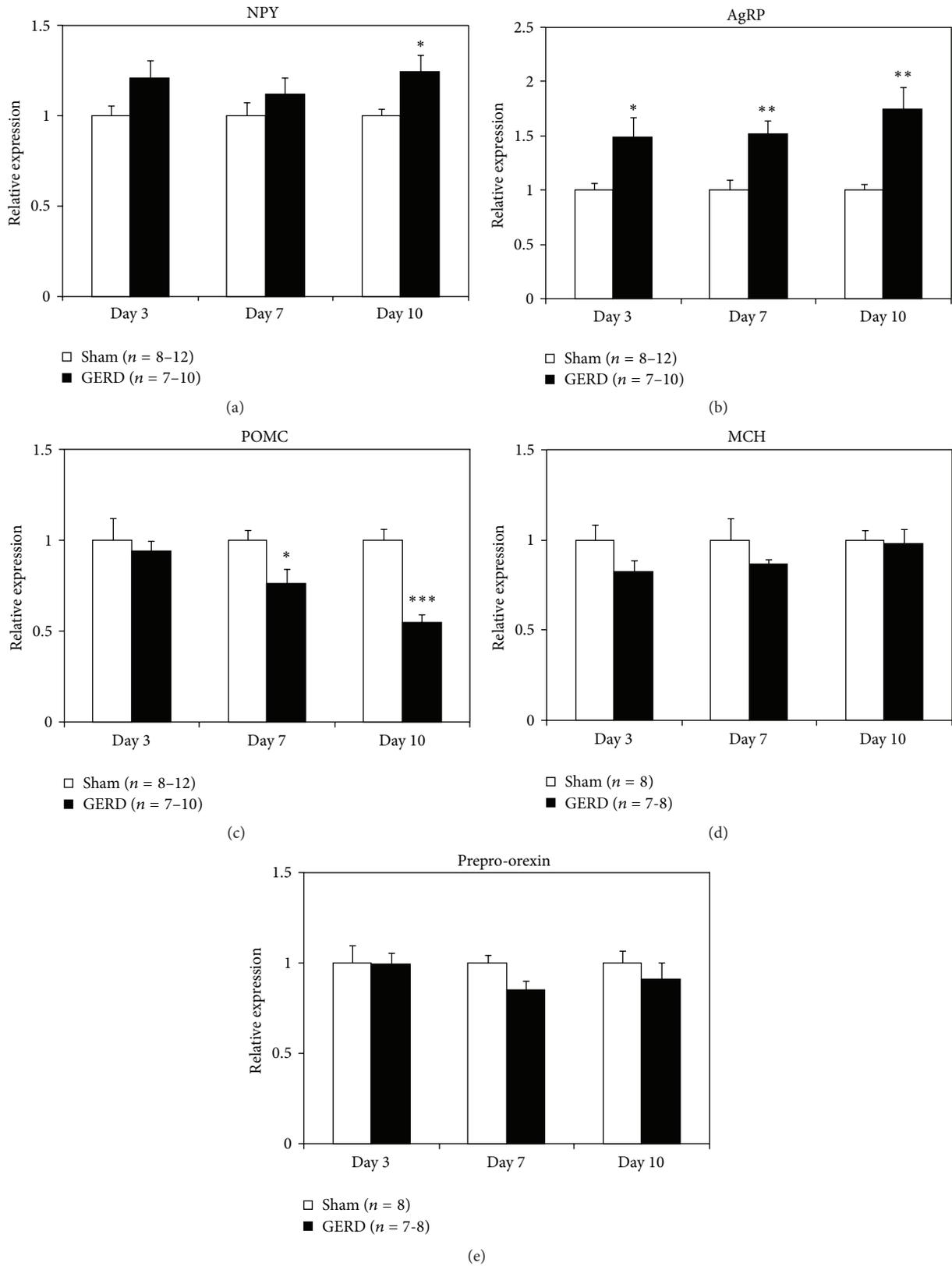


FIGURE 5: Hypothalamic mRNA expression in sham-operated and GERD rats on days 3, 7, and 10 after GERD induction. (a) Neuropeptide Y (NPY), (b) agouti-related protein (AgRP), (c) proopiomelanocortin (POMC), (d) melanin-concentrating hormone (MCH), and (e) prepro-orexin mRNA expression. \*, \*\*, and \*\*\* $P < 0.05$ , 0.01, and 0.001 versus sham-operated rats on each day.

administration of acyl ghrelin at a dose of 3 nmol/rat to sham-operated rats increased food intake significantly [12]. In normal rats, administration of ghrelin at a dose of 1.5 nmol/rat also increased food intake significantly [13]. Food intake did not increase with repeated administration of ghrelin; therefore, GERD rats may require a higher dose of exogenous ghrelin.

The mechanism whereby peripheral blood ghrelin levels are increased in GERD rats is not well understood. There were no differences in relation to prepro-ghrelin or GHS-R mRNA expression in the stomach between sham-operated and GERD rats. These results were not caused by an increase in ghrelin synthesis in the stomach and do not necessarily promote the synthesis of receptors that would increase signal responsiveness. Moreover, expression of the gene encoding GOAT, which is an enzyme that adds an octanoyl group to proghrelin, was significantly decreased. This result is in accordance with the findings that GOAT mRNA may be negatively regulated during long-time fasting [14]. This may be due to negative feedback as a result of abundant acyl ghrelin present in the peripheral blood. Therefore, ghrelin secretion from the stomach may contribute to the high peripheral blood ghrelin levels.

GHS-R is a G-protein-coupled receptor, and these receptors typically undergo depolarization after ligand binding [15]. Sustained high plasma ghrelin levels in GERD rats may cause systemic GHS-R depolarization. However, in this study we found that hypothalamic NPY/AgRP mRNA expression significantly increased from day 3 in GERD rats compared with that in sham-operated rats. Ghrelin binds to GHS-R at the end of the vagus nerve in the stomach, stimulates NPY/AgRP neurons present in the hypothalamic arcuate nucleus, and increases NPY/AgRP mRNA expression [3, 13]. Because NPY/AgRP mRNA expression is increased in GERD rats, ghrelin signaling may be maximal. Leptin inhibits NPY/AgRP expression, stimulates POMC neurons, and produces POMC mRNA [16, 17]. Since plasma leptin was only examined on day 10 after surgery, we can only suggest that increased ghrelin levels were inversely correlated with plasma leptin levels. However, in addition to the increased plasma ghrelin levels, decreased plasma leptin levels might have contributed to increased NPY/AgRP and significantly reduced POMC mRNA expression in GERD rats.

In this study, prepro-orexin and MCH mRNA expression was not altered in GERD rats. The orexigenic signal, via the activation of the NPY/AgRP neurons, is transmitted to the LH, leading to the activation of orexin or MCH neurons [18–21]. Orexin and MCH are primarily synthesized in the LH when these neurons are activated. MCH-1R antagonism or depletion of the peptide results in hypophagia, and MCH-1R-deficient mice are lean [22–24]. It is well known that a reward system, including appetite or learning, is mediated by activation of these neurons via the dopamine neurons [25, 26] in the ventral tegmental area or nucleus accumbens. We speculated that orexin or MCH neuron activation might be suppressed in GERD rats, leading to the inhibition of food intake. However, a detailed mechanism of action and the identity of the factors that cause suppression of these neurons

is still unknown. Further study is needed to clarify why orexin or MCH neurons are unresponsive.

Currently, there exists no GERD model that suitably reflects human GERD. The model presented in the current experiment describes an extensive operation involving ligation of the forestomach and fixing of a ring to the pyloric region, making it differ greatly from human GERD. Furthermore, although these are preliminary results, administration of an effective dose of PPI [27] did not affect initial body weight, food intake, or ghrelin concentration in GERD rats. It is possible to conclude that overexposure of the esophagus to stomach acid is not involved in the increased secretion of ghrelin or abnormal food intake-related factor expression. Moreover, because oral administration of Cisapride clearly improved gastric emptying in the present model [12], it appears that treatment with a pyloric region ring and ligation does not cause an irreversible reduction in gastric motility. However, the possibility that extensive surgery affects food intake-related parameters could not be excluded. The validity of the GERD model used in this study needs to be sufficiently verified in the future. In addition, the effect of physical impairment and stomach acid exposure in surgery on food intake-related parameters and hormone levels needs to be carefully examined.

## 5. Conclusion

In comparison to normal rats, GERD rats characteristically have increased peripheral acyl ghrelin levels, decreased leptin levels, and might have impaired ghrelin signal transmission. However, it remains necessary to verify the validity of the model used and to further examine details regarding PPI administration.

## Conflict of Interests

There is no conflict of interests with any financial organization regarding the material discussed in the paper.

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