JOURNAL OF EDUCATION, HEALTH AND SPORT
eISSN 2391-8306 · Open Access · Peer-reviewed
apcz.umk.pl/JEHS · Nicolaus Copernicus University in Toruń

Cite as: JANKOWSKI, Gabriela, SIEMASZKO, Kai, BADRAN, Mahmoud, KOLADZYN, John, JANKOWSKI, Marianna, WASILEWSKI, Luiza, TWOMBLY, Gregory, MARGIELEWSKA, Weronika and SŁODYCZKA, Anna. Diagnostic Challenges in Unusual Causes of Refractory GERD-Like Symptoms. Journal of Education, Health and Sport. 2026;91:70866. https://doi.org/10.12775/JEHS.2026.91.70866

ARTICLE TIMELINE
Received: 14.04.2026 Revised: 15.05.2026
Accepted: 16.05.2026 Published: 23.05.2026

INDEXING & EVALUATION
MEiN points: 40 Unique ID: 201159
Disciplines: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences).

The journal has been awarded 40 points in the parametric evaluation by the Polish Ministry of Higher Education and Science (Annex to the announcement of 05.01.2024, No. 32318). Unique Journal Identifier: 201159. Scientific disciplines: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences).

Punkty Ministerialne z 2019 – aktualny rok 40 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 Lp. 32318. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).

Diagnostic Challenges in Unusual Causes of Refractory GERD-Like Symptoms

Authors:

Jankowski Gabriela

0009-0001-0897-8017

gabriela.jankowski@gmail.com

University Clinical Hospital in Bialystok ul. M. C. Skłodowskiej 24a, 15-276 Białystok,

Poland

Siemaszko Kai

0009-0007-2772-8981

Kai.siemaszko@outlook.com

University Clinical Hospital in Bialystok ul. M. C. Skłodowskiej 24a, 15-276 Białystok, Poland

Badran Mahmoud

0009-0005-6234-2537

Mahmoudbadran.md@gmail.com

University Clinical Hospital in Bialystok ul. M. C. Skłodowskiej 24a, 15-276 Białystok, Poland

Koladzyn John

0009-0000-9237-7355

JohnKoladzyn@gmail.com

University Clinical Hospital in Bialystok ul. M. C. Skłodowskiej 24a, 15-276 Białystok, Poland

Jankowski Marianna

0009-0008-4178-3546

marianna.jankowski@gmail.com

University Clinical Hospital in Bialystok ul. M. C. Skłodowskiej 24a, 15-276 Białystok, Poland

Wasilewski Luiza

0009-0000-0324-4949

wasilewskiluiza@gmail.com

University Clinical Hospital in Bialystok ul. M. C. Skłodowskiej 24a, 15-276 Białystok, Poland

Twombly Gregory

0009-0008-4847-8587

Matt-twombly@hotmail.com

University Clinical Hospital in Bialystok ul. M. C. Skłodowskiej 24a, 15-276 Białystok, Poland

Margielewska Weronika

0009-0003-1466-3980

we.margielewska@gmail.com

University Clinical Hospital in Bialystok ul. M. C. Skłodowskiej 24a, 15-276 Białystok, Poland

Słodyczka Anna

0009-0007-8687-2270

aslodyczka.md@gmail.com

University Clinical Hospital in Bialystok ul. M. C. Skłodowskiej 24a, 15-276 Białystok, Poland

Abstract:

Background: Refractory gastroesophageal reflux disease (GERD) describes persistent reflux-like symptoms despite optimized proton pump inhibitor therapy and is frequently driven by alternative or overlapping pathologies rather than uncontrolled acid exposure.

Aim: To review unusual causes of refractory GERD-like symptoms, with emphasis on pathophysiology, diagnostic pitfalls, and practical evaluation strategies for achalasia, eosinophilic esophagitis, belching and rumination disorders, gastroparesis, and Zollinger-Ellison syndrome (ZES).

Material and methods: A review of selected literature was conducted using the PubMed database. The search was performed using keywords including “refractory GERD,” “PPI refractory,” “achalasia,” “gastroparesis,” “esophageal motility disorders,” and “case reports”.

Results: Achalasia, eosinophilic esophagitis, behavioural belching and rumination, gastroparesis, and gastrinoma-driven acid hypersecretion all produce GERD-like complaints yet require distinct diagnostic tools such as high-resolution manometry, esophageal biopsies, impedance-pH monitoring, gastric emptying studies, and fasting gastrin measurement. Failure to recognize these entities risks inappropriate escalation of antireflux therapy, unnecessary surgery, and progression to complications.

Conclusions: Systematic physiologic and endoscopic evaluation of PPI-refractory symptoms is essential to uncover uncommon causative conditions, align therapy with underlying mechanisms, and prevent mislabeling patients with simple GERD when they harbour distinct motility, inflammatory, behavioural, or neuroendocrine disorders.

Key words: refractory GERD; esophageal motility disorders; eosinophilic esophagitis; belching; rumination syndrome; gastroparesis; Zollinger-Ellison syndrome.

1. Introduction

Gastroesophageal reflux disease (GERD) involves reflux of gastric contents into the esophagus, causing troublesome symptoms and/or complications confirmed by esophagitis or abnormal esophageal acid exposure on pH monitoring [1]. Refractory GERD features persistent symptoms despite optimized acid-suppressive therapy, such as twice-daily proton pump inhibitors (PPIs) for at least 8 weeks [2,3]. These patients often report atypical symptoms like belching, chest pain, and globus sensation, alongside heightened anxiety, somatic complaints, and reduced quality of life [4,5].

1.1 Pathophysiology of GERD

GERD results from the failure of the lower esophageal sphincter (LES), which typically plays a role in protecting and preventing gastric contents from refluxing into the esophagus [6]. Transient LES relaxations (TLESRs), mediated by vagal pathways and triggered by gastric distension, account for most reflux events, especially postprandially [7,8]. Hiatal hernia disrupts the esophagogastric junction (EGJ) barrier, reducing LES-crural diaphragm synergy and promoting acid pocket formation above the diaphragm [9,10].

Ineffective esophageal motility impairs primary and secondary peristalsis, prolonging refluxate clearance and worsening acid exposure [8,10]. Reduced salivary bicarbonate and mucosal resistance exacerbate injury from acid, pepsin, bile, and weakly acidic reflux [7]. In refractory cases, esophageal hypersensitivity amplifies symptom perception despite optimized therapy [4].

1.2 Prevalence and Burden

Refractory GERD affects 20-40% of GERD cases, imposing significant healthcare costs and diagnostic challenges due to overlapping conditions [9,11,12]. As a result, GERD and refractory GERD has become the most common given diagnosis in GI practices [13]. Atypical presentations complicate management, as symptoms may stem from non-acid reflux, motility issues, or functional disorders rather than uncontrolled acid [10,14]. Timely identification of underlying causes improves outcomes and prevents complications like strictures or Barrett's esophagus [15].

2. Unusual Causes

Unproven refractory GERD requires off-therapy evaluation with endoscopy, pH-impedance, and manometry to confirm pathology and exclude mimics [4,14]. Key unusual etiologies include:

- **Achalasia**: Impaired LES relaxation mimics regurgitation; high-resolution manometry shows absent peristalsis [10,14],
- **Eosinophilic esophagitis (EoE)**: Eosinophil infiltration causes dysphagia/heartburn; endoscopy/biopsy reveals rings/furrows (>15 eos/HPF) [15,16],
- **Zollinger-Ellison syndrome (ZES)**: Hypergastrinemia from gastrinoma leads to refractory ulcers/esophagitis; elevated fasting gastrin diagnoses [17,18],

- **Belching/rumination**: Supragastric belching or rumination causes aerophagia/reflux-like symptoms; impedance-pH detects air influx [19, 20],
- **Gastroparesis**: Delayed emptying triggers reflux; scintigraphy confirms; overlaps with dyspepsia [21,22].

2.1 Achalasia

Achalasia is a primary esophageal motility disorder that may masquerade as refractory GERD. Manifestations of achalasia include progressive dysphagia for solids and liquids, regurgitation, heartburn, and non cardiac chest pain [23].

Achalasia is defined by impaired relaxation of the esophagogastric junction and absent or disordered peristalsis, leading to functional outflow obstruction and esophageal stasis rather than true gastroesophageal reflux [23,24]. This stasis may lead to fermentation of retained contents, generating GERD-like regurgitation and chest pain rather than true acid reflux [7,9].

In the specific context of refractory GERD-like symptoms, achalasia should be excluded with objective motility testing before any escalation to invasive antireflux therapies [7,9,10,14]. High-resolution manometry using Chicago Classification v4.0 is the gold standard, diagnosing achalasia by a persistently elevated integrated relaxation pressure with absent peristalsis and further subtyping into types I, II and III based on pressurization and spasticity patterns [9,24]. When manometry shows absent contractility with borderline relaxation pressures, supportive tests such as a timed upright barium esophagogram and functional lumen imaging probe are recommended, since classic radiographic features like a bird's beak narrowing and retained column of contrast, together with low esophagogastric junction distensibility, help distinguish achalasia or esophagogastric junction outflow obstruction from severe hypomotile GERD [9,24].

Endoscopy remains essential as an initial test in patients with refractory heartburn or regurgitation to document or refute erosive esophagitis, Barrett's esophagus and peptic strictures as objective evidence for or against GERD [7, 9]. In achalasia, however, endoscopy is often macroscopically normal early and may only show subtle clues such as a dilated, fluid-filled or food-filled esophagus, resistance at the cardia or specific signs including rosette folds, the Gingko leaf configuration and the pinstripe mucosal pattern in more advanced disease [15,24].

2.2 Eosinophilic esophagitis

The pathophysiology of eosinophilic oesophagitis (EoE) is intricate, as it involves genetic predisposition, environmental exposures, and immune system dysregulation [25]. EoE is an immune mediated type 2 inflammatory disease of the oesophagus typically driven by food and aeroallergens that induce a Th2 response with key roles for IL 4, IL 5, IL 13, thymic stromal lymphopoietin and eotaxin 3 [25,26]. Genetic susceptibility involves variants in genes regulating epithelial barrier and immune activation, including CAPN14, TSLP and filaggrin, which interact with environmental exposures to promote disease [25].

Epithelial barrier dysfunction with loss of junctional proteins facilitates allergen penetration, sustaining eosinophilic inflammation and leading over time to tissue remodelling, fibrosis, reduced distensibility and a fibrostenotic phenotype that manifests as dysphagia and strictures [16, 25, 27]. Manometric findings in EoE are heterogeneous and range from normal peristalsis to ineffective oesophageal motility, absent contractility and hypercontractile patterns such as distal oesophageal spasm, nutcracker and jackhammer oesophagus, reflecting inflammatory injury and remodelling of muscle and neural structures [16,27].

EoE frequently presents with dysphagia, food impaction and sometimes heartburn or chest discomfort, and was historically often misdiagnosed as GERD because symptoms and oesophageal eosinophilia can overlap in both conditions [25,27,28]. It is important to note that EoE may coexist with GERD, therefore patients may require treatment of both conditions concurrently [28]. Chronic EoE related remodelling and dysmotility can produce persistent upper gastrointestinal symptoms that mimic refractory GERD, including ongoing heartburn, chest pain and regurgitation despite acid suppression [14,16,25,27].

Current EoE diagnostic criteria require symptoms of oesophageal dysfunction plus at least 15 eosinophils per high power field in oesophageal biopsies, after exclusion of other causes of oesophageal eosinophilia [29]. Because mucosal changes may be subtle or even endoscopically normal, multiple biopsies from different oesophageal levels are recommended in patients with refractory GERD like symptoms, particularly when dysphagia or food impaction is present [16,25,27].

2.3 Belching and Rumination

Belching disorders and rumination syndrome are disorders of gut-brain interaction that frequently mimic refractory GERD and can lead to inappropriate escalation of acid-suppressive or surgical therapy if unrecognized [14,20].

Gastric belching is a physiological venting of swallowed air from the stomach via transient lower esophageal sphincter relaxations, whereas supragastric belching is a learned behaviour in which air is sucked or swallowed into the esophagus and immediately expelled without reaching the stomach [19]. Rumination syndrome is characterized by postprandial, effortless regurgitation of

recently ingested food due to voluntary abdominal wall and diaphragmatic contractions that abruptly raise intragastric pressure and overcome the lower esophageal sphincter [30]. High-resolution impedance manometry confirms that these events are active motor patterns, distinct from passive acid reflux, with stereotyped rises in gastric pressure and rapid retrograde flow into the proximal esophagus [20].

In patients labeled as PPI-refractory GERD, postprandial impedance-manometry studies identify pathological supragastric belching in about 40% and rumination in about 20%, indicating that behavioral aerophagia and regurgitation are common explanations for persistent "reflux" symptoms [14]. A reflux-center series highlights that such patients often present with troublesome belching, regurgitation and multiple upper-GI complaints, and that belching disorders and rumination are typical pitfalls during selection for antireflux surgery [20]. Impedance-pH case data further show tight temporal association between clusters of supragastric and gastric belches, air swallows, reflux episodes and symptoms such as hiccups, illustrating how disordered air handling alone can reproduce GERD-like symptom complexes [31]. Population data confirm that excessive belching disorders and rumination are not rare in the general population, supporting routine consideration of these entities in refractory GERD-like presentations [19,30].

Since atypical symptoms such as supragastric belching and rumination can imitate reflux, appropriate esophageal physiologic testing plays a critical role in the clinical evaluation and management of esophageal disorders [32]. Current complex GERD algorithms recommend targeted physiologic testing to distinguish true refractory GERD from belching and rumination disorders before intensifying therapy or offering surgery [14]. Twenty-four hour impedance-pH monitoring differentiates gastric from supragastric belching by the direction and origin of gas-related impedance changes and quantifies supragastric belching burden in patients with prominent belching or regurgitation [19]. Postprandial high-resolution impedance manometry identifies rumination by demonstrating characteristic R-wave intragastric pressure rises preceding retrograde flow, separating primary rumination from reflux-driven secondary patterns [20]. Ambulatory impedance-pH with symptom association analysis can link esophageal air events to both typical and atypical complaints, helping to reclassify many presumed refractory GERD cases as behavioral belching or rumination syndromes that require cognitive-behavioral and diaphragmatic breathing interventions rather than further acid suppression [19,30,31].

2.4 Gastroparesis

Gastroparesis is defined as objectively delayed gastric emptying with symptoms such as postprandial fullness, early satiety, nausea, vomiting, bloating and upper abdominal pain, most commonly idiopathic, diabetic or postsurgical [33]. Normal emptying requires fundic accommodation, antral trituration and coordinated pyloric relaxation; antral hypomotility and pyloric dysfunction (for example pylorospasm) disrupt this sequence and promote gastric retention [34]. At a cellular level, full-thickness biopsies show loss and ultrastructural injury of

interstitial cells of Cajal, altered neuromuscular signaling including reduced neuronal nitric oxide synthase in some diabetic patients, and macrophage-driven immune dysregulation with oxidative stress targeting the gastric pacemaker apparatus [34,35].

Motor and cellular abnormalities in gastroparesis lead to persistent gastric distension and impaired clearance of ingested material, which can coexist with or mimic GERD-like complaints such as “reflux,” belching and upper abdominal discomfort [34,35]. Symptom profiles often overlap with functional dyspepsia, and many patients are not distinguishable by symptoms or low-fat test meal emptying, which contributes to under-recognition in patients initially labeled as having refractory reflux [21,34]. A case report in an older adult with pyloric stenosis illustrates that structural gastric outlet obstruction can produce a gastroparesis-like picture with massive gastric distension and may increase the risk of regurgitation and aspiration in patients with pre-existing GERD [36].

When a patient has persistent reflux-like symptoms despite adequately dosed PPI therapy, and these are accompanied by postprandial fullness, nausea, vomiting, or bloating, gastroparesis can be considered as an alternative or concomitant diagnosis. Retrospective cohort data indicate that approximately 5.8% of PPI non-responders are ultimately diagnosed with gastroparesis on gastric emptying scintigraphy, even though they report chest pain, heartburn, and regurgitation that are clinically indistinguishable from typical GERD presentations [37]. In such patients, formal evaluation for delayed gastric emptying can be considered after endoscopy and reflux testing, particularly when symptoms remain unexplained or appear disproportionate to objective esophageal findings.

2.5 Zollinger-Ellison Syndrome

Zollinger-Ellison syndrome (ZES) is caused by gastrin-secreting neuroendocrine tumors gastrinomas that induce marked gastric acid hypersecretion, classically leading to GERD, peptic ulcer disease and chronic diarrhea [38]. Gastrin stimulates enterochromaffin-like cells to release histamine and drives parietal cell hydrochloric acid overproduction, which in turn produces severe peptic injury in the esophagus, stomach, duodenum and sometimes proximal jejunum [39,40].

ZES is an uncommon but clinically relevant cause of refractory GERD-like symptoms because gastrin-secreting tumors drive marked gastric acid hypersecretion that can overwhelm otherwise standard PPI regimens [17]. Up to 31% of patients can present initially with GERD symptoms, and nearly half have GERD at first evaluation, often together with abdominal pain or diarrhea [41]. The chronic hypergastrinemia increases both basal and maximal acid output by inducing parietal cell hyperplasia, so even a structurally normal antireflux barrier is exposed to an overwhelming acid load [41]. In this context, refractoriness reflects tumor-mediated hypergastrinemia rather than primary failure of the antireflux barrier, so symptom control usually

requires higher-than-conventional acid suppression and definitive management of the gastrinoma [17].

Patients with refractory GERD who continue to have acid related manifestations despite adequate PPI therapy, should be evaluated for ZES, especially if they have a history of PUD, chronic diarrhea or weight loss. Routine gastric acid analysis is now rarely available, and widespread PPI use complicates diagnosis because 80-100% of non-ZES patients on PPIs develop hypergastrinemia, sometimes exceeding four- to ten-fold, mimicking the biochemical profile of ZES [42]. At the same time, PPIs are potent enough to control symptoms in most ZES patients at standard GERD/PUD doses, so the historical "red flag" of failure on H2-receptor antagonists is no longer seen [42]. For patients with refractory GERD-like symptoms, especially when accompanied by chronic diarrhea, weight loss, severe or recurrent ulcers or advanced esophageal injury, early measurement of fasting gastrin and systematic evaluation for ZES are essential to avoid prolonged mislabeling as simple GERD [43].

3. Summary

Refractory GERD-like symptoms frequently arise from conditions in which heartburn, regurgitation, or chest pain are driven by mechanisms other than persistent acid reflux, including achalasia, eosinophilic esophagitis, belching and rumination syndromes, gastroparesis, and Zollinger-Ellison syndrome. These entities share substantial symptom overlap with classical GERD, yet differ markedly in pathophysiology and required investigations, so reliance on empirical acid suppression alone risks prolonged misdiagnosis and delays in definitive care. Careful use of high-resolution manometry, impedance-pH monitoring, targeted esophageal biopsies, gastric emptying studies, and biochemical testing is therefore essential to discriminate between true refractory GERD and its mimics in daily practice.

Conclusions

Unusual causes of refractory GERD-like symptoms are sufficiently prevalent and clinically impactful that they should be actively sought whenever patients fail to respond to adequately dosed proton pump inhibitor therapy. A structured, physiology-based diagnostic approach that integrates endoscopy with manometry, impedance–pH monitoring, motility assessment, and endocrine evaluation can uncover achalasia, eosinophilic esophagitis, behavioural belching and rumination, gastroparesis, or Zollinger-Ellison syndrome before escalation to invasive antireflux interventions. Recognizing and treating these distinct mechanisms improves symptom control, prevents complications such as strictures, aspiration, or severe peptic injury, and ultimately optimizes outcomes for patients labeled with refractory GERD.

Disclosure

Author's contribution

Conceptualization: Gabriela Jankowski

Methodology: Marianna Jankowski, Mahmoud Badran

Formal analysis: Luiza Wasilewski, Weronika Margielewska

Investigation: Gregory Twombly, Marianna Jankowski

Writing-original draft preparation: Gabriela Jankowski, John Koladzyn

Writing-review and editing: John Koladzyn, Kai Siemaszko, Gregory Twombly, Luiza Wasilewski, Weronika Margielewska

Supervision: Mahmoud Badran, Anna Słodyczka

Funding - No specific funding was received for this work.

All authors have read and agreed to the published version of the manuscript.

Financing statement

This research received no external funding.

Institutional Review Board Statement

Not applicable.

Informed Consent Statement

Not applicable.

Data Availability Statement

Not applicable.

Conflict of Interest

The authors deny any conflict of interest.

References

[1] Katz PO, Dunbar KB, Schnoll-Sussman FH, Greer KB, Yadlapati R, Spechler SJ. ACG Clinical Guideline for the Diagnosis and Management of Gastroesophageal Reflux Disease. Am J

Gastroenterol. 2022 Jan 1;117(1):27-56. doi: 10.14309/ajg.0000000000001538. PMID: 34807007; PMCID: PMC8754510.

[2] Yadlapati R, DeLay K. Proton Pump Inhibitor-Refractory Gastroesophageal Reflux Disease. Med Clin North Am. 2019 Jan;103(1):15-27. doi: 10.1016/j.mcna.2018.08.002. Epub 2018 Nov 1. PMID: 30466671; PMCID: PMC6260943.

[3] Wang G, Zhu C, Yin J. Etiology and treatment options for refractory gastroesophageal reflux disease: A scope review. Clinics (Sao Paulo). 2025 Jan-Dec;80:100763. doi: 10.1016/j.clinsp.2025.100763. Epub 2025 Sep 20. PMID: 40976133; PMCID: PMC12489830.

[4] Davis TA, Gyawali CP. Refractory Gastroesophageal Reflux Disease: Diagnosis and Management. J Neurogastroenterol Motil. 2024 Jan 30;30(1):17-28. doi: 10.5056/jnm23145. PMID: 38173155; PMCID: PMC10774805.

[5] Zhang N, Wang Y, Fang SS, Han M, Zheng QW, Zhu YY, Zhang MY, Li JJ, Cui LX, Tian JL, Deng YH, Zhu SL, Ni HM, Zhou L, Zuo GL, Huang TS, Liao Q, Li XQ, Shang YY, Wang YJ, Tian Y, Ge LY, Han HQ, Hu WM, Jiang Y, Li YJ, Mao X, Yang LH, Yao JM, Zheng X, Wang HW, Fang SQ. Clinical characteristics and risk factors of refractory gastroesophageal reflux disease: A multicenter cross-sectional study. World J Gastroenterol. 2025 Dec 7;31(45):113060. doi: 10.3748/wjg.v31.i45.113060. PMID: 41378325; PMCID: PMC12686995.

[6] Bucan JI, Braut T, Krsek A, Sotosek V, Baticic L. Updates in Gastroesophageal Reflux Disease Management: From Proton Pump Inhibitors to Dietary and Lifestyle Modifications. Gastrointestinal Disorders. 2025; 7(2):33. https://doi.org/10.3390/gidisord7020033

[7] Valdovinos Díaz MA, Amieva-Balmori M, Carmona-Sánchez R, Coss-Adame E, Gómez-Escudero O, González-Martínez M, Huerta-Iga F, Morel-Cerda E, Remes-Troche JM, Tamayo-de la Cuesta JL, Torres-Villalobos G, Valdovinos-García LR, Vázquez-Elizondo G, Villar-Chávez AS, Arenas-Martínez JA. Good clinical practice recommendations for the diagnosis and treatment of gastroesophageal reflux disease. An expert review from the Asociación Mexicana de Gastroenterología. Rev Gastroenterol Mex (Engl Ed). 2024 Jan-Mar;89(1):121-143. doi: 10.1016/j.rgmxen.2023.12.002. Epub 2024 Apr 4. PMID: 38580493.

[8] Lin S, Li H, Fang X. Esophageal Motor Dysfunctions in Gastroesophageal Reflux Disease and Therapeutic Perspectives. J Neurogastroenterol Motil. 2019 Oct 30;25(4):499-507. doi: 10.5056/jnm19081. PMID: 31587540; PMCID: PMC6786454.

[9] Vayal-Veettil A, Gyawali CP. Diagnosis and Management of Gastroesophageal Reflux Disease: Current Insights. Clin Exp Gastroenterol. 2025 Jul 8;18:149-162. doi: 10.2147/CEG.S507237. PMID: 40656590; PMCID: PMC12255250.

[10] Lei WY, Yi CH, Liu TT, Hung JS, Wong MW, Chen CL. Esophageal motor abnormalities in gastroesophageal reflux disorders. Tzu Chi Med J. 2024 Mar 26;36(2):120-126. doi: 10.4103/tcmj.tcmj_209_23. PMID: 38645779; PMCID: PMC11025585.

[11] Ganesh Shashi B, Hafsa SN. Current Advances in Diagnosis, Therapeutics, and Surgical Interventions for the Management of Refractory Gastroesophageal Reflux Disease (GERD): An

Update. Cureus. 2024 Sep 9;16(9):e69001. doi: 10.7759/cureus.69001. PMID: 39385893; PMCID: PMC11463874.

[12] Labenz J, Schoppmann SF. Improving treatment of people with gastro-esophageal reflux disease refractory to proton pump inhibitors. Commun Med (Lond). 2024 Oct 14;4(1):200. doi: 10.1038/s43856-024-00632-6. PMID: 39397153; PMCID: PMC11471847.

[13] Kahrilas PJ, Keefer L, Pandolfino JE. Patients with refractory reflux symptoms: What do they have and how should they be managed? Neurogastroenterol Motil. 2015 Sep;27(9):1195-201. doi: 10.1111/nmo.12644. PMID: 26303047; PMCID: PMC4551076.

[14] Snyder DL, Katzka DA. Complex Gastroesophageal Reflux Disease. Gastro Hep Adv. 2022 Apr 5;1(3):420-430. doi: 10.1016/j.gastha.2022.02.014. PMID: 39131678; PMCID: PMC11307939.

[15] Hosaka H, Kuribayashi S, Itoi Y, Sato K, Tanaka H, Takeuchi Y, Uraoka T. The Role of Endoscopy in Gastroesophageal Reflux Disease. Digestion. 2025 Sep 24:1-9. doi: 10.1159/000548088. Epub ahead of print. PMID: 40991519.

[16] Chai C, Krishnan U. Dysmotility in Eosinophilic Esophagitis. Front Pediatr. 2022 Feb 28;10:853754. doi: 10.3389/fped.2022.853754. PMID: 35295702; PMCID: PMC8918583.

[17] Fernicola A, Parmeggiani D, Crocetto F, Calogero A, Cece A, Romano D, Benassai G, Quarto G, Santangelo M. Esophageal Perforation in Zollinger-Ellison Syndrome: A Scoping Review of Management and Outcomes. JGH Open. 2026 Jan 22;10(1):e70323. doi: 10.1002/jgh3.70323. PMID: 41585576; PMCID: PMC12827053.

[18] Bentley B, Chanaa F, Clayton S. Complete Esophageal Obstruction: A Rare Complication of Zollinger-Ellison Syndrome. ACG Case Rep J. 2023 Nov 15;10(11):e01205. doi: 10.14309/crj.0000000000001205. PMID: 38025843; PMCID: PMC10651347.

[19] Sawada A, Fujiwara Y, Sifrim D. Belching in Gastroesophageal Reflux Disease: Literature Review. J Clin Med. 2020 Oct 20;9(10):3360. doi: 10.3390/jcm9103360. PMID: 33092195; PMCID: PMC7590068.

[20] Eypasch E, Ebner M, Leers J. The Unusual Patient in a Reflux Center: Belching, Rumination, Somatization as Pitfalls of Patient Selection for Anti-Reflux Surgery. Visc Med. 2025 Mar 11:1-6. doi: 10.1159/000545089. Epub ahead of print. PMID: 40330637; PMCID: PMC12052369.

[21] Kim BJ, Kuo B. Gastroparesis and Functional Dyspepsia: A Blurring Distinction of Pathophysiology and Treatment. J Neurogastroenterol Motil. 2019 Jan 31;25(1):27-35. doi: 10.5056/jnm18162. PMID: 30509017; PMCID: PMC6326193.

[22] Tavakkoli A, Sayed BA, Talley NJ, Moshiree B. Acid and non-acid reflux in patients refractory to proton pump inhibitor therapy: is gastroparesis a factor? World J Gastroenterol. 2013 Oct 7;19(37):6193-8. doi: 10.3748/wjg.v19.i37.6193. PMID: 24115816; PMCID: PMC3787349.

[23] Subedi D, Parajuli BR, Bista N, Rauniyar S, Dhonju K, Bhusal S, Aryal E, Adhikari D, Aryal S, Karna A. Achalasia cardia: A case report in young female. Clin Case Rep. 2024 Aug 5;12(8):e9239. doi: 10.1002/ccr3.9239. PMID: 39104735; PMCID: PMC11298990.

[24] Pesce M, Pagliaro M, Sarnelli G, Sweis R. Modern Achalasia: Diagnosis, Classification, and Treatment. J Neurogastroenterol Motil. 2023 Oct 30;29(4):419-427. doi: 10.5056/jnm23125. PMID: 37814432; PMCID: PMC10577462.

[25] Farah A, Assaf T, Hindy J, Abboud W, Mahamid M, Savarino EV, Mari A. The Dynamic Evolution of Eosinophilic Esophagitis. Diagnostics (Basel). 2025 Jan 21;15(3):240. doi: 10.3390/diagnostics15030240. PMID: 39941170; PMCID: PMC11816659.

[26] Erdle SC, Carr S, Chan ES, Robertson K, Watson W. Eosinophilic esophagitis. Allergy Asthma Clin Immunol. 2024 Dec 19;20(Suppl 3):72. doi: 10.1186/s13223-024-00929-0. PMID: 39702284; PMCID: PMC11660462.

[27] Arora AS, Yamazaki K. Eosinophilic esophagitis: asthma of the esophagus? Clin Gastroenterol Hepatol. 2004 Jul;2(7):523-30. doi: 10.1016/s1542-3565(04)00236-8. PMID: 15224275.

[28] Wąsik J, Małecka-Wojciesko E. Eosinophilic Esophagitis-What Do We Know So Far? J Clin Med. 2023 Mar 14;12(6):2259. doi: 10.3390/jcm12062259. PMID: 36983260; PMCID: PMC10051236.

[29] Reed CC, Dellon ES. Eosinophilic Esophagitis. Med Clin North Am. 2019 Jan;103(1):29-42. doi: 10.1016/j.mcna.2018.08.009. Epub 2018 Nov 1. PMID: 30466674; PMCID: PMC6260964.

[30] Sawada A, Fujiwara Y. Belching Disorders and Rumination Syndrome: A Literature Review. Digestion. 2024;105(1):18-25. doi: 10.1159/000534092. Epub 2023 Oct 16. PMID: 37844547.

[31] Woodley FW, Williams K, Di Lorenzo C, Michel HK. Significant Temporal Association of Esophageal Air Events (Supragastric Belches, Air Swallows, and Gastric Belches) With Hiccups: A Case Study in an Adolescent. JPGN Rep. 2022 Jun 21;3(3):e209. doi: 10.1097/PG9.0000000000000209. PMID: 37168628; PMCID: PMC10158523.

[32] Gyawali CP, Carlson DA, Chen JW, Patel A, Wong RJ, Yadlapati RH. ACG Clinical Guidelines: Clinical Use of Esophageal Physiologic Testing. Am J Gastroenterol. 2020 Sep;115(9):1412-1428. doi: 10.14309/ajg.0000000000000734. PMID: 32769426; PMCID: PMC9468980.

[33] Stojek M, Jasiński T. Gastroparesis in the intensive care unit. Anaesthesiol Intensive Ther. 2021;53(5):450-455. doi: 10.5114/ait.2021.110959. PMID: 34816707; PMCID: PMC10172955.

[34] Camilleri M, Sanders KM. Gastroparesis. Gastroenterology. 2022 Jan;162(1):68-87.e1. doi: 10.1053/j.gastro.2021.10.028. Epub 2021 Oct 27. PMID: 34717924; PMCID: PMC8678360.

[35] Grover M, Farrugia G, Stanghellini V. Gastroparesis: a turning point in understanding and treatment. Gut. 2019 Dec;68(12):2238-2250. doi: 10.1136/gutjnl-2019-318712. Epub 2019 Sep 28. PMID: 31563877; PMCID: PMC6874806.

[36] R Sousa B, Rodrigues TB, Ribeiro J. When the Stomach Takes a Vacation: The Unseen Battles of Gastroparesis. Cureus. 2024 Mar 16;16(3):e56263. doi: 10.7759/cureus.56263. PMID: 38623117; PMCID: PMC11017365.

[37] Galindo G, Vassalle J, Marcus SN, Triadafilopoulos G. Multimodality evaluation of patients with gastroesophageal reflux disease symptoms who have failed empiric proton pump inhibitor therapy. Dis Esophagus. 2013 Jul;26(5):443-50. doi: 10.1111/j.1442-2050.2012.01381.x. Epub 2012 Aug 2. PMID: 22862422.

[38] Rossi RE, Elvevi A, Citterio D, Coppa J, Invernizzi P, Mazzaferro V, Massironi S. Gastrinoma and Zollinger Ellison syndrome: A roadmap for the management between new and old therapies. World J Gastroenterol. 2021 Sep 21;27(35):5890-5907. doi: 10.3748/wjg.v27.i35.5890. PMID: 34629807; PMCID: PMC8475006.

[39] Shaik MR, Shaik NA, Kunarathnam V, Bilgrami Z, Wheeler E, Hu S. Esophageal Perforation Unveiling the Diagnosis of Zollinger-Ellison Syndrome. J Community Hosp Intern Med Perspect. 2023 Sep 2;13(5):77-81. doi: 10.55729/2000-9666.1228. PMID: 37868662; PMCID: PMC10589047.

[40] Efared B, Tassiou EIM, Bako ABA, Boubacar I, Boureima HS, Nouhou H. Sporadic Zollinger-Ellison syndrome in a patient with isolated mesenteric gastrinoma. Int J Surg Case Rep. 2024 Mar;116:109474. doi: 10.1016/j.ijscr.2024.109474. Epub 2024 Mar 5. PMID: 38447521; PMCID: PMC10926117.

[41] Holzheimer RG, Mannick JA, editors. Surgical Treatment: Evidence-Based and Problem-Oriented. Munich: Zuckschwerdt; 2001. PMID: 21028753.

[42] Jensen RT, Ramos-Alvarez I, Norton JA. Current Medical Controversies in Zollinger-Ellison Syndrome. Biomedicines. 2025 Dec 11;13(12):3051. doi: 10.3390/biomedicines13123051. PMID: 41463062; PMCID: PMC12730841.

[43] Klimko A, Plotogea O, Constantinescu A, Constantinescu G. Delayed Management of Zollinger-Ellison Syndrome in a Noncompliant Patient. Cureus. 2020 Jun 6;12(6):e8471. doi: 10.7759/cureus.8471. PMID: 32642376; PMCID: PMC7336717.