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Review

Management of Treatment-Resistant Gastroesophageal Reflux: Current Diagnostic and Therapeutic Approaches

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ABSTRACT

Treatment-resistant gastroesophageal reflux (TR-GER), defined as the persistence of typical or atypical GER symptoms despite correct full-dose proton-pump inhibitor (PPI) therapy for at least eight weeks, is a clinical problem that affects up to 40 % of patients treated for GERD and has a substantial impact on quality of life and health-care costs. Its pathophysiology is multifactorial, encompassing non-acid reflux, esophageal hypersensitivity, motility disorders and poor medication adherence. This article critically reviews the evidence on the diagnosis and management of TR-GER, emphasizing the need for a stratified approach that combines clinical reassessment, complementary tests (pH-impedance monitoring, high-resolution manometry and endoscopy) and personalized therapies. Optimization of PPIs, sequential use of H_2 antagonists, prokinetics and visceral pain modulators constitute additional pharmacologic options. Endoscopic procedures such as radiofrequency (Stretta) and transoral incisionless fundoplication (TIF) and surgical interventions, especially laparoscopic Nissen fundoplication, provide high long-term efficacy when appropriately indicated. Non-pharmacologic strategies such as weight loss, head-of-bed elevation, a Mediterranean-style diet and smoking cessation should be part of every therapeutic plan. Recent evidence from randomized trials and meta-analyses supports early integration of multidisciplinary care, aiming not only at symptom control but also at preventing complications such as severe erosive esophagitis and Barrett's esophagus. Successful management of TR-GER depends on a systematic, patient-centered algorithm guided by objective reflux markers and continuous research is needed to improve available pharmacologic and minimally invasive therapies. New immediate-release PPI formulations, nitric-oxide generators and duodenogastric reflux inhibitors represent promising research avenues that may expand the therapeutic arsenal in the coming years.

Keywords: Gastroesophageal reflux; Treatment-resistant; PPIs; Clinical management; Surgical therapy

Introduction

Gastroesophageal reflux (GER) is one of the most prevalent gastrointestinal diseases worldwide, with estimates ranging from 10 % to 20 % in Western populations and a growing trend in emerging countries[1]. Although most cases respond satisfactorily to lifestyle modifications combined with proton-pump inhibitors (PPIs), up to 40 % of patients remain symptomatic after eight to twelve weeks of correct PPI use, characterizing treatment-resistant gastroesophageal reflux (TR-GER)[2]. Therapeutic resistance is multifactorial. Pathophysiological studies show that many patients labeled as refractory actually have weak or non-acid reflux, esophageal hypersensitivity or functional brain-esophagus axis disorders, conditions in which acid suppression alone is insufficient[3].

Diagnostic errors such as mistaking eosinophilic esophagitis, achalasia or severe dysmotility for GER and low adherence to medication significantly contribute to persistent symptoms[4]. Parallel to elucidating these mechanisms, the last decade has witnessed the advent of high-resolution diagnostic technologies that precisely characterize reflux nature and esophageal motor behavior. Twenty-four-hour multichannel intraluminal impedance-pH monitoring detects reflux episodes regardless of pH and temporally correlates them with patient-reported symptoms[5].

High-resolution esophageal manometry provides detailed parameters of peristalsis and lower esophageal sphincter (LES) pressure, allowing identification of specific motor disorder sub-phenotypes. These advances have shaped new assessment algorithms based on objective patient stratification. Therapeutically, the arsenal for TR-GER has expanded considerably. Beyond dose adjustment and split dosing of PPIs, several pharmacologic classes have been incorporated into treatment algorithms: nocturnal H_2-receptor antagonists ("breakthrough acid" strategy), prokinetics that accelerate gastric emptying and reduce transient LES relaxations and central neuromodulators that modulate esophageal pain perception[6]. Consequently, constructing evidence-based clinical protocols to guide decision-making and deliver personalized, mechanism-targeted care has become imperative.

Objectives

This article aims to provide a comprehensive review of recent literature on TR-GER, describing the judicious use of complementary tests and targeted selection of therapeutic alternatives. The economic impact of TR-GER on health systems and the emerging role of minimally invasive endoscopic interventions as a bridge or alternative to classic ant reflux surgery are also discussed.

Materials and Methods

A literature review was conducted using the PubMed, SciELO, Google Scholar and ScienceDirect databases.

Discussion

Discussion of TR-GER management must begin by recognizing that not every refractory patient truly has persistent pathologic reflux. In prospective series employing impedance-pH monitoring in symptomatic individuals on PPIs, only one-third showed a positive correlation between reflux episodes and symptoms[2]. This underscores the importance of systematic evaluation, starting with confirming adherence and optimizing PPI dosing administering the drug 30 minutes before the first meal and, if necessary, in a double dose. Those with genuine pharmacologic failure are candidates for stepped therapy. An initial step includes double-dose or immediate-release PPIs combined with nocturnal H_2 antagonists, a strategy that reduces "breakthrough acid" in up to 70 % of cases[6].

If symptoms persist, adding a prokinetic such as domperidone or prucalopridemay be useful, especially in patients with delayed gastric emptying. Recent meta-analyses show a significant reduction in total acid exposure time when prokinetics are combined with PPIs[7]. Patients with negative pH monitoring and a high symptom index fit the hypersensitive esophagus profile; in these cases, low-dose tricyclic antidepressants or serotonin-noradrenaline reuptake inhibitors reduce pain scores by more than 50 %. When severe motor disorders such as failed peristalsis or absent contractions are documented, procedures that increase LES pressure should be avoided, prioritizing pharmacologic therapies or corrective motility surgery.

Endoscopic interventions have emerged as an intermediate option between pharmacotherapy and surgery. Radiofrequency (Stretta) produces collagen remodeling and increases basal LES tone; randomized trials demonstrate a sustained 2.5-point symptom score reduction after 48 months, with low complication rates[8]. Transoral incisionless fundoplication (TIF) creates a 270° valve endoscopically, yielding symptom relief comparable to laparoscopic fundoplication at three-year follow-up. Antireflux surgery remains the gold standard for patients with documented acid reflux and partial PPI response. Laparoscopic Nissen fundoplication achieves satisfaction rates exceeding 85 % at ten years[9], although complications such as dysphagia and gas-bloat syndrome must be considered. Magnetic sphincter augmentation (LINX®) offers a promising alternative, preserving physiologic gastric anatomy and being reversible.

A dimension still under-explored in TR-GER involves duodenogastroesophageal reflux, rich in bile acids. Conventional pH monitoring detects only acid reflux; thus, alkaline events may remain hidden, causing persistent inflammation[10]. Studies using alkaline impedance-pH monitoring show that up to 20 % of refractory patients exhibit prolonged bile exposure. In such cases, adding sucralfate or ursodeoxycholic acid and, if unsuccessful, definitive surgery may be beneficial. Finally, lifestyle measures remain essential. Ten-percent weight loss reduces reflux frequency by 32 %, an effect potentiated by a Mediterranean diet[11]. Head-of-bed elevation, avoiding meals three hours before bedtime and smoking cessation complete the recommended non-pharmacologic approach[4].

Conclusion

TR-GER requires precise diagnosis, individualized therapy and active patient participation. Apparent PPI failure may stem from non-adherence, motor disorders or visceral hypersensitivity; therefore, tests such as impedance-pH monitoring and high-resolution manometry are mandatory before advanced therapies[3]. A stepped algorithm includes pharmacologic adjustments, neuromodulation, endoscopic procedures (Stretta, TIF) and laparoscopic antireflux surgery, with magnetic devices as an emerging alternative[9].

Future prospects include drugs that modulate transient LES relaxations, bile reflux inhibitors and remote esophageal pH sensors. Although technology advances, lifestyle measures remain a fundamental pillar. Weight loss, a Mediterranean diet, smoking cessation and correct PPI intake timing reduce recurrence and complications[11].

Multidisciplinary programs integrating gastroenterologists, surgeons, nutritionists and psychologists shorten the time to definitive diagnosis and improve patient satisfaction. Public health policies focusing on obesity and sedentary behavior may reduce the incidence of symptomatic GER and, consequently, TR-GER. By combining robust science, appropriate technology and health education, the challenge of TR-GER can be transformed into an opportunity for person-centered care, promoting durable symptom relief and restoration of quality of life[12-15].

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