



# **GASTROESOPHAGEAL REFLUX DISEASE (GERD): A DIAGNOSTIC ALGORITHMS, PATHOPHYSIOLOGY MODELS, AND THERAPEUTIC STRATEGIES**

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## **Abstract:**

Gastroesophageal reflux disease (GERD) is a chronic, relapsing, and heterogeneous gastrointestinal disorder characterized by retrograde flow of gastric contents into the esophagus, leading to typical symptoms (heartburn, regurgitation) and/or mucosal and extra-esophageal complications. Its global prevalence is steadily increasing due to rising obesity rates, dietary pattern changes, sedentary lifestyle, aging populations, and increasing prevalence of hiatal hernia and metabolic syndrome. GERD represents a major burden on healthcare systems due to reduced quality of life, chronic medication use, and risk of complications such as erosive esophagitis and Barrett's esophagus.

To provide a comprehensive, structured, evidence-based synthesis of GERD, including its pathophysiology, clinical phenotypes, diagnostic algorithms, therapeutic strategies, long-term management outcomes, and regionally adapted considerations with emphasis on resource-limited settings such as Uzbekistan (Andijan region).

This structured narrative review integrates evidence from major international guidelines including ACG 2025 clinical guidelines, AGA clinical updates, the Lyon Consensus, randomized controlled trials, systematic reviews, and meta-analyses. Additionally, emerging expert consensus trends and anticipated 2025 updates in GERD diagnosis and management were incorporated to reflect current and near-future clinical practice directions.

GERD is increasingly recognized as a spectrum disorder comprising erosive esophagitis (ERD), non-erosive reflux disease (NERD), reflux hypersensitivity, and functional heartburn. Pathophysiology involves transient lower esophageal sphincter relaxations, impaired esophagogastric junction barrier function, delayed gastric emptying, and esophageal hypersensitivity. Diagnosis requires a multimodal approach combining clinical symptom assessment, upper endoscopy, ambulatory pH or pH-impedance monitoring, and esophageal high-resolution manometry. Proton pump inhibitors (PPIs) remain the cornerstone of therapy, achieving symptom control in approximately 70–85% of patients and mucosal healing rates up to 90% in erosive disease. However, 30–40% of patients exhibit partial or non-response, requiring phenotype-based stratification and personalized management. Lifestyle modification, including weight reduction, dietary adjustment, and head-of-bed elevation, provides adjunctive benefit. Emerging therapeutic approaches include alginate-based formulations, neuromodulators for hypersensitive phenotypes, and minimally invasive endoscopic or surgical interventions such as fundoplication and transoral incisionless procedures.

GERD is a multifactorial and phenotypically diverse disorder that requires a precision medicine approach supported by objective diagnostic testing and individualized treatment strategies. Future management



paradigms emphasize early phenotypic classification, rational PPI use, integration of non-acid reflux management, and adaptation of international guidelines to regional healthcare realities, particularly in countries such as Uzbekistan where diagnostic resources and specialist access may be limited.

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**Keywords:**

**INTRODUCTION**

Gastroesophageal reflux disease (GERD) is one of the most prevalent chronic gastrointestinal disorders worldwide and represents a major cause of outpatient visits in gastroenterology and primary care. It is characterized by the retrograde flow of gastric contents into the esophagus, leading to a broad spectrum of esophageal and extra-esophageal symptoms and complications. GERD significantly reduces patient quality of life, affecting sleep, daily functioning, work productivity, and psychological well-being.

From an epidemiological perspective, GERD demonstrates a wide global distribution with an estimated prevalence ranging from 10% to 30% in Western countries and a rising incidence in many Asian and developing regions. This increasing trend is strongly associated with modern lifestyle changes, including increased obesity rates, sedentary behavior, high-fat dietary patterns, tobacco use, alcohol consumption, and aging populations. In addition, the rising prevalence of hiatal hernia and metabolic syndrome further contributes to disease burden.

Global burden and healthcare impact GERD represents a substantial socioeconomic burden due to: High prevalence and chronic relapsing course, Long-term dependence on acid-suppressive therapy, Frequent outpatient consultations and diagnostic procedures, Significant direct and indirect healthcare costs

In many healthcare systems, GERD is among the most frequently diagnosed gastrointestinal conditions, and its complications, such as erosive esophagitis, peptic strictures, Barrett's esophagus, and esophageal adenocarcinoma, contribute to long-term morbidity and mortality risk.

Pathophysiological background GERD is no longer considered a single uniform disease but rather a heterogeneous disorder of esophagogastric junction dysfunction. Key mechanisms include transient lower esophageal sphincter relaxations, impaired antireflux barrier function, delayed gastric emptying, esophageal hypersensitivity, and impaired mucosal defense mechanisms. These mechanisms explain the wide variability in symptom presentation and therapeutic response.

Clinical and diagnostic significance The diagnosis of GERD remains complex due to the lack of a single gold standard test. Clinical evaluation must integrate symptom assessment, endoscopic findings, functional testing (pH or pH-impedance monitoring), and esophageal motility studies. The heterogeneity of the disease has led to the development of phenotype-based classifications that guide individualized therapy.

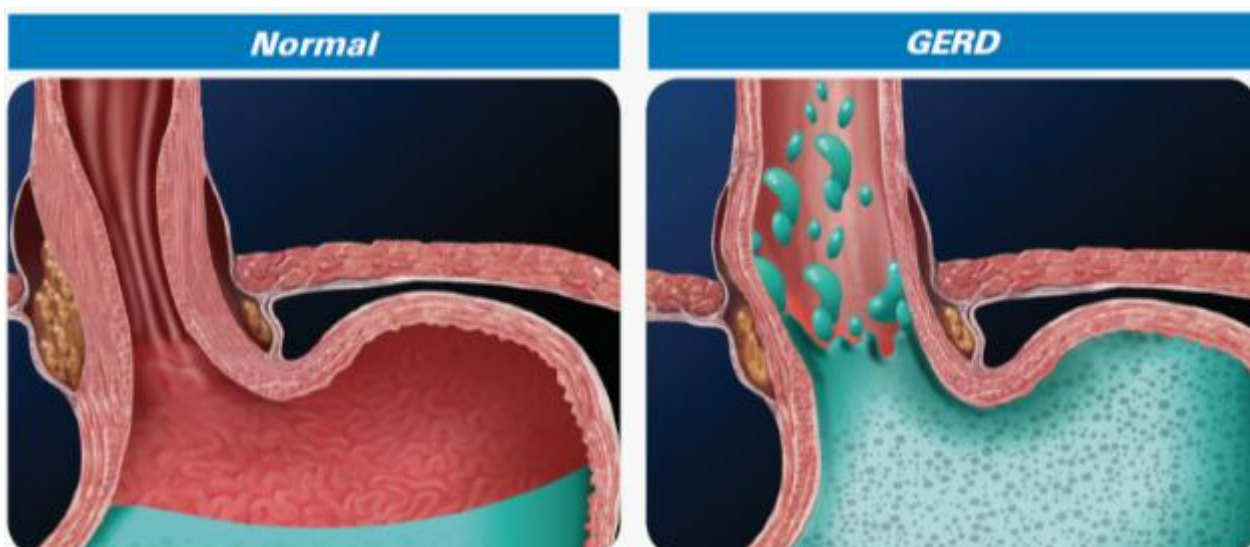
Regional perspective (Uzbekistan and Andijan region) In Uzbekistan, including the Andijan region, GERD is increasingly recognized in clinical practice; however, it remains underdiagnosed and often managed empirically. Contributing factors include limited access to advanced diagnostic modalities such as pH-impedance monitoring and high-resolution manometry, as well as delayed referral to specialized gastroenterology services. Lifestyle factors such as high-carbohydrate diets, rising obesity prevalence, and irregular dietary habits further contribute to disease occurrence.

Conceptual framework Contemporary understanding emphasizes GERD as a spectrum disorder rather than a single entity. This includes erosive reflux disease (ERD), non-erosive reflux disease (NERD), reflux hypersensitivity, and functional heartburn. Each phenotype demonstrates distinct pathophysiological mechanisms and requires tailored diagnostic and therapeutic approaches.

Overall, GERD remains a major global health challenge requiring early recognition, accurate phenotyping, and individualized management strategies supported by evidence-based guidelines and adapted to regional healthcare capacities.

**METHODS**

This study is designed as a structured narrative IMRAD review focusing on gastroesophageal reflux disease (GERD), integrating current evidence-based clinical guidelines, high-quality clinical trials, and emerging consensus recommendations. The methodology follows established standards for narrative synthesis of biomedical literature with emphasis on diagnostic, therapeutic, and regional healthcare perspectives.



This work is a structured narrative IMRAD (Introduction–Methods–Results–Discussion) review. The review synthesizes current global evidence on GERD pathophysiology, clinical phenotypes, diagnostic algorithms, and management strategies. Unlike a systematic review with quantitative meta-analysis, this design allows integration of heterogeneous evidence sources including guidelines, randomized controlled trials, observational studies, and expert consensus statements.

A comprehensive literature search and evidence synthesis was performed using the following major sources:

American College of Gastroenterology (ACG) Clinical Guidelines (2022 and 2025 emerging updates)

American Gastroenterological Association (AGA) Clinical Practice Updates (2025 updates)

Lyon Consensus on GERD diagnostics (updated expert interpretations and extensions)

Randomized controlled trials (RCTs) published between 2000 and 2025 evaluating pharmacologic, endoscopic, and surgical interventions for GERD

Systematic reviews and meta-analyses from major gastroenterology journals

Key studies on proton pump inhibitors (PPIs), alginate therapy, neuromodulators, and anti-reflux surgery

Regional clinical observations relevant to Central Asia, with emphasis on Uzbekistan and the Andijan region

Studies and publications were included based on the following criteria:

Studies involving adult patients with clinically suspected or objectively confirmed GERD

Research evaluating pharmacologic therapies (PPIs, H<sub>2</sub>-receptor antagonists, alginates, prokinetics, neuromodulators)

Clinical trials assessing surgical or endoscopic anti-reflux interventions

Studies focusing on diagnostic accuracy, including endoscopy, pH-metry, pH-impedance monitoring, and high-resolution manometry

Articles published in peer-reviewed journals in English or Russian languages

Evidence-based clinical guidelines and consensus statements from recognized gastroenterology societies  
Exclusion Criteria (added for methodological completeness)

Case reports with insufficient diagnostic confirmation, Studies lacking clear GERD diagnostic criteria, Non-peer-reviewed publications without clinical validation, Pediatric-only studies (unless directly relevant to transitional physiology concepts), The collected evidence was qualitatively synthesized using a thematic approach, focusing on: Pathophysiological mechanisms, Diagnostic stratification models, Phenotype-based classification systems, Treatment efficacy outcomes, Regional applicability of international guidelines in resource-limited settings such as Uzbekistan

## RESULTS

Gastroesophageal reflux disease (GERD) demonstrates a wide and heterogeneous global distribution with significant geographic, socioeconomic, and lifestyle-related variability. Its prevalence has shown a steady upward trend over the past three decades, particularly in urbanized and industrialized regions.

Global prevalence Western countries: 15–25%  
Northern Europe & North America: up to 20–30% in selected populations  
Asia-Pacific region: 5–15% (but

rapidly increasing) Middle East: 10–20% Global pooled estimate: approximately 13–20%

Trends over time Continuous increase over the last 20–30 years Strong correlation with obesity epidemic Increased detection due to improved awareness and endoscopic access

Age and sex distribution Peak incidence: 40–70 years Slight male predominance in erosive disease Non-erosive reflux disease (NERD) more common in females

**Risk factors (quantitative clinical impact)**

Obesity (BMI >30)	██████████	(Very high risk)
Hiatal hernia	██████████	(High risk)
Smoking	██████████	
Alcohol consumption	██████████	
High-fat diet	██████████	
Pregnancy	██████████	
Sedentary lifestyle	██████████	
Metabolic syndrome	██████████	

The increasing prevalence of GERD correlates strongly with: Rising abdominal obesity → increased intra-abdominal pressure, Increased transient lower esophageal sphincter relaxations, Higher prevalence of hiatal hernia in aging populations

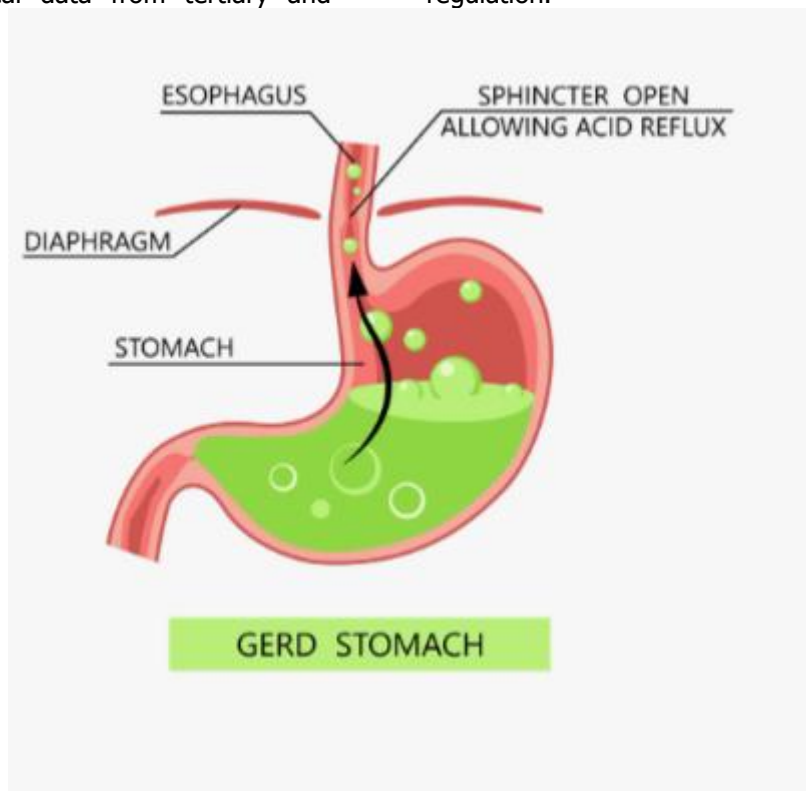
Regional epidemiology: Uzbekistan (Andijan region) Although population-based epidemiological studies are limited, clinical data from tertiary and

primary care settings in Uzbekistan suggest: Increasing GERD symptom burden in urban regions such as Andijan, Higher prevalence of symptomatic reflux in middle-aged adults, Strong association with dietary patterns rich in carbohydrates and fats, Underdiagnosis due to limited access to pH-impedance and HRM testing, High rate of empirical proton pump inhibitor (PPI) use without objective confirmation

Healthcare utilization impact, GERD accounts for a significant proportion of gastroenterology outpatient visits, Increasing use of endoscopy for dyspepsia and reflux symptoms, Rising economic burden due to chronic PPI therapy and repeated consultations

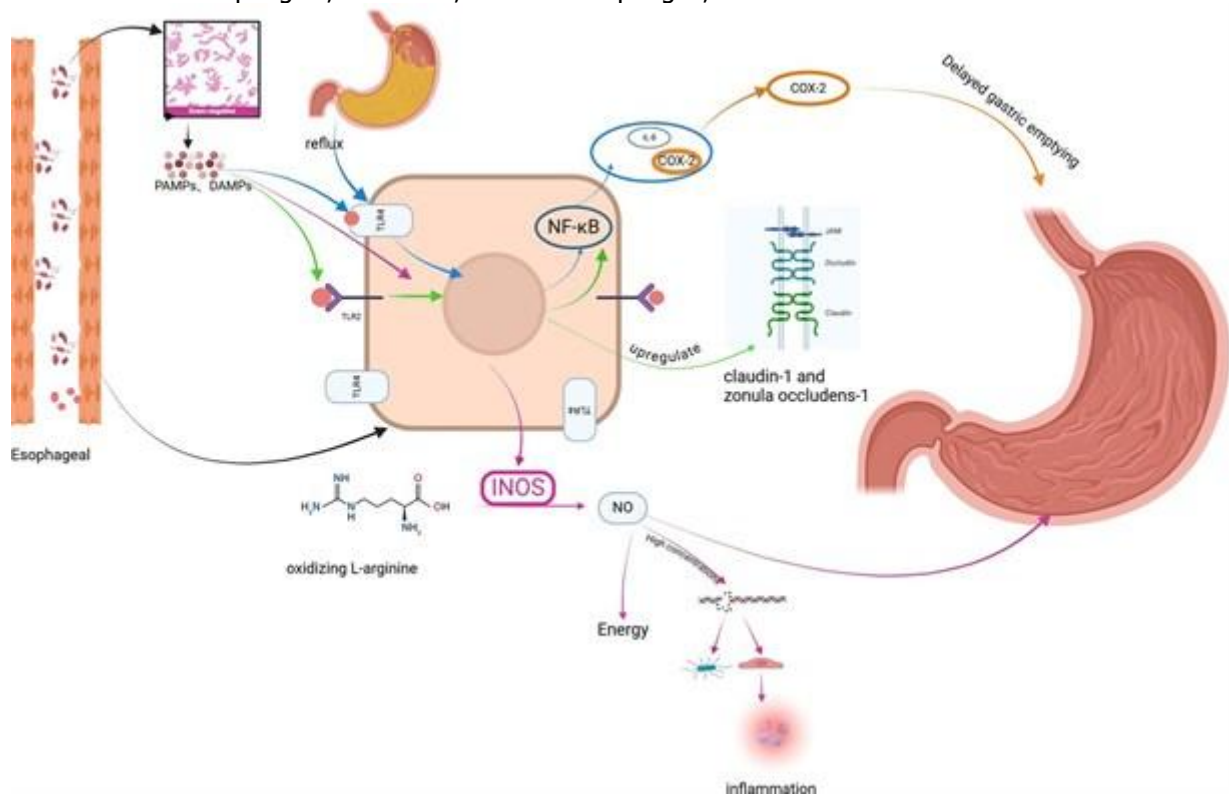
GERD should be considered a modern lifestyle-associated chronic disease with multifactorial etiology, increasing prevalence, and significant regional variation. In Central Asia, including Uzbekistan, the disease is likely underdiagnosed but clinically significant, requiring improved diagnostic pathways and population-based studies.

GERD is a multifactorial disorder resulting from a complex interaction between mechanical barrier dysfunction, chemical injury, impaired esophageal clearance, and altered mucosal and neural sensitivity. Contemporary understanding considers GERD not only as an acid-related disease but also as a disorder of the esophagogastric junction and neurogastroenterological regulation.



**Diagram 1: GERD Mechanism Flow (Expanded Pathophysiology Model)**

Genetic predisposition + lifestyle + obesity  
 ↓  
 Impaired esophagogastric junction integrity  
 (LES dysfunction + Hiatal hernia)  
 ↓  
 ↑ Transient LES relaxations (TLESRs)  
 ↓  
 Increased gastric pressure / delayed emptying  
 ↓  
 Pathologic reflux episodes (acid + pepsin + bile salts)  
 ↓  
 Esophageal mucosal barrier disruption  
 (dilated intercellular spaces)  
 ↓  
 Activation of inflammatory cascade  
 (IL-6, TNF- $\alpha$ , IL-8, cytokines)  
 ↓  
 Oxidative stress + epithelial injury  
 ↓  
 Peripheral + central sensitization  
 (visceral hypersensitivity)  
 ↓  
 Clinical phenotypes: Heartburn, Regurgitation, Chest pain  
 Extra-esophageal symptoms  
 ↓  
 Complications: Erosive esophagitis, Strictures, Barrett's esophagus, Adenocarcinoma risk





**Esophagogastric Junction (EGJ) Dysfunction**

The primary mechanical defect in GERD is incompetence of the esophagogastric junction, which includes: Lower esophageal sphincter (LES) hypotension, Disruption of diaphragmatic crura support, Hiatal hernia formation increasing reflux susceptibility. These abnormalities reduce the barrier pressure preventing gastric contents from entering the esophagus.

Transient Lower Esophageal Sphincter Relaxations (TLESRs) are the most important physiological mechanism responsible for reflux episodes in GERD. They are vagally mediated reflex relaxations of the LES unrelated to swallowing and are triggered by gastric distension. In GERD patients, frequency and duration of TLESRs are significantly increased.

Refluxate contains multiple injurious components: Gastric acid (HCl): primary corrosive agent, Pepsin: proteolytic enzyme active at low pH. Bile acids: contribute to non-acid reflux injury. Combined exposure leads to epithelial damage, loss of tight junction integrity, and increased mucosal permeability.

Mucosal Barrier Dysfunction Esophageal mucosal defense is impaired through: Dilated intercellular spaces, Reduced bicarbonate secretion, Impaired epithelial restitution, Reduced mucosal blood flow, This enhances susceptibility even to weakly acidic reflux.

Inflammatory and Immune Activation Chronic reflux induces activation of inflammatory pathways: IL-6, TNF- $\alpha$ , IL-1 $\beta$  upregulation Recruitment of immune cells (neutrophils, eosinophils in overlap cases) Chronic low-grade inflammation contributing to tissue remodeling

GERD symptoms are strongly influenced by: Peripheral esophageal hypersensitivity Central sensitization in brain-gut axis Altered pain perception thresholds This explains symptom persistence in NERD and functional heartburn despite minimal acid exposure.

The interaction of acid exposure and sensory response results in four major clinical phenotypes: Erosive reflux disease (ERD), Non-erosive reflux disease (NERD), Reflux hypersensitivity, Functional heartburn GERD pathophysiology is a multi-level process involving mechanical, chemical, inflammatory, and neurogenic factors. This complexity explains variable clinical presentation, diagnostic challenges, and heterogeneous treatment response across patients and populations.

Contemporary GERD classification is based on a phenotype-driven model that integrates endoscopic findings, physiologic acid exposure, and symptom-reflux correlation. This approach enables personalized management and improves treatment outcomes, particularly in patients with PPI-refractory symptoms.

**Table 1: Phenotypic Classification of GERD**

Phenotype	Endoscopy	pH-impedance test	Symptom severity	Reflux correlation
Erosive Reflux Disease (ERD)	Positive (erosions)	Abnormal acid exposure	Severe	Positive
Non-Erosive Reflux Disease (NERD)	Normal	Abnormal acid exposure	Moderate-severe	Positive
Reflux Hypersensitivity	Normal	Normal acid exposure	High symptom burden	Positive symptom-reflux association
Functional Heartburn	Normal	Normal acid exposure	Variable	No correlation

ERD is characterized by visible mucosal breaks on upper endoscopy due to chronic acid exposure. Patients typically present with severe heartburn and regurgitation. This phenotype shows strong response to proton pump inhibitors (PPIs) with mucosal healing rates up to 90%.

NERD represents the most common GERD phenotype. Despite normal endoscopic findings, patients demonstrate pathological acid exposure on pH monitoring. Symptom severity may be similar to ERD; however, mucosal injury is absent. Treatment response to PPIs is variable (50–70%).

In this phenotype, acid exposure is within normal limits; however, there is a strong temporal association between reflux events and symptom perception. Pathophysiology is primarily driven by visceral hypersensitivity and neurogastroenterological dysfunction. Neuromodulators and pain modulators are often required in addition to acid suppression therapy.

Functional heartburn is defined by the absence of pathological acid exposure and lack of symptom-reflux correlation. Symptoms are driven by central pain processing abnormalities rather than gastroesophageal reflux. Patients do not respond to PPIs and require



neuromodulator-based or behavioral therapy approaches.

Phenotype-based classification is critical for:  
Selecting appropriate therapy (PPI vs neuromodulators)  
Avoiding unnecessary long-term acid suppression  
Identifying patients for anti-reflux surgery  
Predicting treatment response

Phenotyping requires integration of: Upper endoscopy (mucosal assessment) Ambulatory pH or pH-impedance monitoring High-resolution esophageal manometry Symptom association probability (SAP) analysis

In Uzbekistan, phenotypic classification is underutilized due to limited access to advanced diagnostic tools. As a result, many patients are empirically treated with PPIs without confirmation of GERD subtype, leading to potential overuse of acid suppression therapy and underdiagnosis of functional disorders.

GERD is best understood as a spectrum of overlapping phenotypes rather than a single disease entity. Accurate classification significantly improves diagnostic precision and enables individualized, outcome-based treatment strategies.

Gastroesophageal reflux disease (GERD) presents with a broad clinical spectrum ranging from mild intermittent symptoms to severe complications involving esophageal mucosal damage and extra-esophageal manifestations. Clinical presentation depends on disease phenotype, acid exposure severity, and individual visceral sensitivity.

Typical esophageal symptoms include: Heartburn (retrosternal burning sensation) Acid regurgitation Sour or bitter taste in the mouth Postprandial chest discomfort Heartburn is the most common symptom and is often exacerbated by meals, recumbency, bending forward, and late-night eating.

GERD may manifest beyond the esophagus due to microaspiration or vagally mediated reflex mechanisms: Chronic cough Hoarseness / laryngitis Asthma-like symptoms Globus sensation Dental enamel erosion Chronic pharyngitis These manifestations are often misdiagnosed, leading to delayed treatment.

Alarm features requiring urgent endoscopic evaluation: Dysphagia (progressive) Odynophagia Unexplained weight loss Gastrointestinal bleeding (melena, hematemesis) Iron-deficiency anemia Persistent vomiting

GERD severity ranges from mild intermittent symptoms to severe disease with complications: Mild: episodic heartburn, no mucosal damage Moderate: frequent symptoms requiring daily therapy Severe: erosive esophagitis, Barrett's esophagus, strictures

Symptom intensity does not always correlate with mucosal damage. Some patients with severe erosive disease may be asymptomatic, while others with functional heartburn report severe symptoms despite normal investigations.

Symptoms → Risk stratification

↓

Alarm signs?

├ YES → Immediate endoscopy

└ NO

↓

Empirical PPI trial (4–8 weeks)

↓

Response to therapy?

├ YES → Continue / step-down therapy

└ NO

↓

pH-impedance monitoring OFF PPI

↓

Phenotype classification

↓

Targeted therapy: PPI optimization, Alginate therapy, Neuromodulators, Anti-reflux surgery

**Diagnostic components** Upper endoscopy (EGD) Ambulatory pH or pH-impedance monitoring High-resolution manometry (HRM) Symptom association probability (SAP) Confirm presence of pathological reflux Identify GERD phenotype Exclude alternative diagnoses Guide individualized therapy

GERD management is phenotype-based and stepwise, combining lifestyle modification, pharmacotherapy, and procedural interventions.

Lifestyle modification Weight reduction (BMI control) Avoid late-night meals ( $\geq 3$  hours before sleep) Head-of-bed elevation Smoking cessation Reduction of fatty, spicy, and acidic foods

First-line therapy: Proton pump inhibitors (PPIs)  
Mechanism: Irreversible inhibition of H<sup>+</sup>/K<sup>+</sup> ATPase  
Efficacy: Symptom control: 70–85% Healing of erosive esophagitis: up to 90% Adjunct therapies: H<sub>2</sub> receptor antagonists Alginate-based formulations

If no response to PPIs: Optimize dosing (timing before meals) Switch PPI class Evaluate adherence Perform pH-impedance testing

Advanced therapies Laparoscopic fundoplication Magnetic sphincter augmentation Endoscopic anti-reflux procedures

GERD represents an emerging but underdiagnosed gastrointestinal condition in Uzbekistan, particularly in the Andijan region, where



healthcare access and diagnostic capabilities vary between urban and rural settings.

Epidemiological characteristics True population prevalence remains unknown due to lack of large-scale studies Increasing clinical incidence in urban centers such as Andijan High-risk lifestyle factors: High-carbohydrate and high-fat diet Rising obesity prevalence Male smoking rates Irregular eating patterns in working populations

Helicobacter pylori interaction High prevalence of H. pylori infection in Uzbekistan Chronic gastritis may alter acid secretion dynamics Post-eradication therapy can unmask latent GERD symptoms Complex bidirectional relationship between H. pylori and reflux disease

Healthcare system in Andijan Endoscopy availability improving in tertiary centers Limited access in rural primary care units pH-impedance and HRM rarely available Heavy reliance on symptom-based diagnosis Frequent empirical PPI prescribing without objective confirmation

## **DISCUSSION**

Gastroesophageal reflux disease (GERD) represents a complex, multifactorial, and clinically heterogeneous disorder that cannot be fully explained by acid exposure alone. Contemporary evidence supports a shift from a traditional acid-centric model to a multidimensional framework incorporating mechanical dysfunction of the esophagogastric junction, esophageal hypersensitivity, impaired mucosal defense, and central nervous system processing abnormalities.

The major clinical challenge in GERD management is heterogeneity in both symptom presentation and treatment response. While proton pump inhibitors (PPIs) remain highly effective in erosive reflux disease (ERD), a substantial proportion of patients (30–40%) experience incomplete symptom relief. This subgroup is often composed of patients with non-erosive reflux disease (NERD), reflux hypersensitivity, or functional heartburn, where acid suppression alone is insufficient.

This heterogeneity necessitates a phenotype-driven approach. Failure to identify underlying phenotypes leads to overtreatment with PPIs, delayed diagnosis of functional disorders, and increased healthcare costs.

A major limitation in GERD diagnosis is the absence of a single gold standard test. Symptom-based diagnosis alone is unreliable due to overlap with functional dyspepsia, cardiac chest pain, and esophageal motility disorders. Therefore, current best practice requires integration of: Upper endoscopy,

Ambulatory pH or pH-impedance monitoring, High-resolution manometry, Symptom association analysis.

However, in resource-limited settings such as Uzbekistan (including Andijan region), access to advanced functional testing is limited. As a result, GERD is frequently diagnosed empirically, leading to misclassification of functional esophageal disorders as reflux disease.

Recent advances highlight the role of transient lower esophageal sphincter relaxations (TLESRs), visceral hypersensitivity, and neuroimmune activation. Cytokine-mediated inflammation (IL-6, TNF- $\alpha$ ) contributes not only to mucosal injury but also to peripheral and central sensitization, explaining persistent symptoms in patients without significant acid exposure.

PPIs remain the cornerstone of therapy; however, their limitations emphasize the need for adjunctive and alternative treatments, including alginate formulations, neuromodulators, and endoscopic or surgical interventions. The future of GERD management lies in precision medicine, where therapy is tailored to individual physiological phenotype rather than symptom presentation alone.

In Uzbekistan, particularly in the Andijan region, GERD management is influenced by healthcare infrastructure limitations. Endoscopy services are available mainly in secondary and tertiary care centers, while pH-impedance monitoring and HRM remain largely unavailable in routine clinical practice.

This creates a diagnostic gap, where many patients are treated empirically without objective confirmation. Additionally, high prevalence of Helicobacter pylori infection may alter gastric acid physiology, complicating clinical interpretation.

Improving diagnostic capacity and implementing standardized clinical pathways are essential to optimize GERD management in this region.

## **CONCLUSION**

GERD is a globally prevalent but regionally variable disease characterized by significant clinical and pathophysiological heterogeneity. It should be considered a spectrum disorder rather than a single uniform condition.

In Uzbekistan, including the Andijan region, GERD represents an emerging clinical burden. Limited access to advanced diagnostic modalities necessitates a pragmatic, resource-adapted approach emphasizing early endoscopy, rational PPI use, and improved referral systems.

A future precision medicine model integrating physiological testing, symptom profiling, and



individualized therapy will significantly improve patient outcomes.

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