Why differences between New York and New Delhi matter in approach to gastroesophageal reflux disease

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Despite rising worldwide prevalence of gastroesophageal reflux disease (GERD), conclusive diagnosis of clinically significant GERD remains elusive, both in New York and in New Delhi. GERD is unique in that diagnosis and management are pursued simultaneously, and indeed, the same diagnostic approach can also be therapeutic, e.g. the proton pump inhibitor (PPI) trial. Currently available tools for GERD diagnosis rely on subjective clinical history or questionnaire data, complemented by objective measures of macroscopic and microscopic mucosal integrity, reflux burden, and esophageal pathophysiology. Consequently, GERD management is nuanced and tailored based on patient factors and each physician's approach to diagnosis, which is unique to each region of the world. However, these diagnostic modalities alone are insufficient for a conclusive diagnosis and must be performed and interpreted within the clinical context, with the understanding that gray areas exist. A multipronged approach increases diagnostic confidence but also requires the insight of the treating physician in choosing the diagnostic and management approach appropriate for each part of the world, hence our heavy reliance on informed consensus opinions from regional thought leaders, which is what the Indian Consensus on GERD provides [1].

Similarities

The fundamental elements of GERD do not change based on geography. At its core, GERD is the reflux of gastric content into the esophagus leading to symptoms, complications, or

both. This broad categorization, previously proposed by the Montreal Consensus [2], has now been endorsed by the Indian Consensus [1]. Both groups acknowledge that body habitus influences reflux burden. In India, where obesity is on the rise, increasing body mass index (BMI) has been shown to positively correlate with increasing rates of clinical GERD [3], an association that has been well documented in the West [4]. This finding argues esophagogastric junction (EGJ) barrier function is essential for maintaining a neutral pH in the esophagus and that physical and physiological alteration of the EGJ in overweight individuals is a universal phenomenon. Similarly, lifestyle factors contribute to GERD everywhere. Smoking, for example, has been linked to reduced lower esophageal sphincter (LES) pressures, decreased saliva production, and adverse effects on the esophageal epithelium; this association with GERD has been documented globally [5, 6].

Entities that mimic GERD are well recognized internationally. The most concerning of these is coronary ischemia. Chest pain can be the only presenting symptom in GERD [7], indistinguishable from angina due to shared innervation [2], making cardiac evaluation imperative prior to GERD evaluation in atypical chest pain. Concern for laryngopharyngeal reflux is worldwide, with a wide array of presenting symptoms ranging from change in voice to frequent throat clearing [8]. Unfortunately, clinical findings are notoriously non-specific and conclusive diagnosis remains difficult everywhere [9]. Non-seasonal asthma with chronic cough should give practitioners from any location pause [10]. Acid exposure contributes to the clinical picture in asthmatics even without classical reflux symptoms, supported by epidemiological data as well as airway hyperreactivity from esophageal acid exposure in animal studies [11]. However, data supporting benefit of treating asymptomatic patients remain incomplete [12]. Eosinophilic esophagitis (EoE) should be considered in patients with refractory GERD symptoms; the Indian tertiary care setting may conform to Western standards rather than the rest of Asia [13] where prevalence, although variable between countries, is estimated to be lower [14]. Finally, when

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GERD symptoms are refractory, it is universally advisable to perform manometry ahead of any surgical intervention as some reports suggest up to a third of such cases are related to diagnoses such as achalasia, supragastric belching, or rumination [15]. The pathophysiology of symptoms in each of these disorders mimicking GERD is universal and therefore shared regardless of geography.

Despite regional differences, there are international mainstays that direct the diagnostic approach. Both Indian and Western standards place the patient's symptoms at the center of GERD diagnosis [2, 16, 17]. It is universally accepted that worrisome, prolonged, or treatment-resistant symptoms be investigated with endoscopy [18]. Evaluation should characterize risk factors such as hiatus hernias, and end organ damage such as esophagitis or Barrett's esophagus (BE), as these allow for increased diagnostic confidence and better treatment efficacy and prognostication [19–21]. Where endoscopic assessment is inconclusive, ambulatory reflux monitoring is a justifiable approach to delineate symptom etiology [20], since this provides a useful reference point for reflux burden across populations when available. Indeed, similar to Western standards [22], Indian studies have also demonstrated the predictive value of ambulatory pH monitoring [23]. Use of global acid exposure standards and availability of modern testing modalities in India add to the concept that pathological reflux thresholds are universal.

Many common sense treatments are universally accepted. First-line management of GERD should include lifestyle modifications including weight loss, elevating the head of the bed, and eliminating identified trigger foods [24, 25]. When these measures are insufficient, H₂-receptor antagonists are reasonable for occasional symptoms, but it is broadly agreed upon that PPIs are superior (Fig. 1) [26]. Despite recent concerns, gastroenterologists worldwide continue to rely on long-term PPI therapy for those with erosive disease, complications such as strictures and BE, and documented reflux responsive to treatment [27, 28]. BE requires lifelong PPI therapy to reduce progression, and high-grade esophagitis requires repeat endoscopy to ensure no occult BE or malignancy exists [29]. Finally, regardless of region, invasive approaches to reflux management should only be carried out in carefully selected patients with conclusive evidence of GERD (Table 1).

Variations

Regional variation in GERD epidemiology is a well-established fact [14, 30, 31], which can impact how GERD is evaluated and managed in different parts of the world. The prevalence of GERD was reported to be 3% to 9% in East Asia, much lower than the 18% to 28% prevalence in the USA, and the 9% to 26% prevalence in Europe [32]. A population-based study reported an 18.5% GERD prevalence in certain regions of India [33], indicating a higher prevalence compared with the Far East

and highlighting the need for appropriate management recommendations. Prevalence in general is increasing in both Western and Asian countries [32], potentially related to the obesity epidemic [34]. Despite this, Asian GERD tends to be predominantly non-erosive, with lower grades of erosive disease even when esophagitis is encountered (Los Angeles [LA] grade A prevalence of 50% to 90% of all erosive esophagitis) [36]. Further, Asian prevalence of BE ($\leq 6\%$ in countries other than Japan) [37] is lower than that reported in Western countries (5% to 15%) [38–40]. Overlap with EoE is lower in Asia compared with Western countries [41], although prevalence in India, as mentioned above, may be higher than in other Asian countries [13]. Consequently, the need for frequent diagnostic screening and surveillance endoscopy to evaluate for erosive esophagitis, BE, and EoE may not be as high in the Indian population.

Attitudes toward and comfort with GERD diagnosis and management also vary across regions, as is evident from the Indian Consensus [1]. There was very high agreement among Indian opinion leaders for the standard definition of GERD, for epidemiologic risk factors including obesity, and for the significance of GERD in affecting quality of life. There was less support for the importance of lifestyle factors (including smoking, alcohol intake, and diet), the effect of posture, and the role of *Helicobacter pylori*. While there was high support for endoscopic findings describing conclusive GERD (erosive esophagitis, hiatus hernia, and BE), confidence in endoscopic description alone for diagnosis of erosive esophagitis was limited, perhaps implying that histopathologic support of the diagnosis could improve confidence. This is not supported by evidence, as even the high-quality blinded expert pathologist review of esophageal biopsies is only modestly effective in making a conclusive GERD diagnosis [42]. While electron microscopy definition of dilated intercellular spaces in the esophageal mucosa can differentiate GERD-related mucosal injury from functional heartburn or normal volunteers [43, 44], this degree of detail in biopsy evaluation is not feasible in clinical settings.

Initial approach to GERD

Some of the important concepts that should guide the approach to GERD are highlighted in the Indian Consensus [1]. A therapeutic trial of acid suppressants when careful history suggests GERD [45] is not only easily available, safe, and clinically effective [46, 47] but also cost-effective in the absence of alarm symptoms [48]. However, guidelines need nuanced interpretation and personalization to each patient's unique situation. For instance, while posture contributes to GERD symptoms, the contribution of posture is most evident when the EGJ is disrupted (hypotensive LES or presence of a hiatus hernia) [49]. Supine acid burden is higher in this setting; therefore, sleeping with the

New York

New Delhi

Fig. 1 Similarities and differences in hierarchy of GERD management between India and Western countries. Standard medical management is similar between both the regions. Confirmation of GERD is imperative prior to escalating to invasive management, and availability determines the diagnostic tests utilized. The more atypical the presenting symptom,

the higher the need for documentation of abnormal GERD metrics prior to long-term GERD management. Options for invasive management are also influenced by local expertise and availability of resources. *LES* lower esophageal sphincter, *GERD* gastroesophageal reflux disease

head end of the bed elevated and avoiding lying down within 1–2 h of eating can reduce nocturnal acid exposure. Similarly, the effects of specific items of diet may be important only if these dietary triggers bring about troublesome symptoms [50]. The more profound dietary contribution to GERD is through weight gain and obesity [51], where the transdiaphragmatic pressure gradient favors reflux due to high intra-abdominal pressures. While there are health benefits in stopping smoking and reducing alcohol intake, including reducing risks of esophageal cancer, direct cause-and-effect benefits in GERD management have not been demonstrated [52, 53]. Therefore, lifestyle approaches need to be tailored to the individual patient's unique GERD presentation, with particular attention paid to weight management in locales where obesity is on the rise.

Several statements relate to atypical GERD symptoms, including asthma, reflux laryngitis, and chest pain, believed to be less prevalent in Asia, compared with Western countries [14]. Among atypical symptoms, chest pain has the highest likelihood of being related to GERD, especially when cardiac etiologies have been excluded. Therefore, a PPI trial may be reasonable in patients with chest pain, in which a symptomatic response can be expected with a sensitivity of 78% and a specificity of 87%

for abnormal acid exposure [54]. Pathologic GERD is less likely with other atypical symptoms; therefore, esophageal physiologic testing has value in determining who needs long-term acid suppression. There was a high degree of agreement for the lack of correlation between laryngoscopic findings and reflux disease in planning GERD management, which is consistent with existing literature [55, 56]. In general, the more atypical the symptom, the higher the need for invasive investigation prior to long-term medical or surgical management of GERD, and the higher the likelihood that invasive investigation will not show evidence for pathologic GERD.

The hierarchy of GERD management starts with lifestyle measures and acid suppression (Fig. 1), which benefit the vast majority of patients with GERD symptoms [57]. If a PPI trial improves GERD symptoms, and no alarm symptoms exist, continuing medical management is more cost-effective than invasive investigation [48], and especially in Asian populations where endoscopy may not provide additional gains, as discussed above [14]. Because of suboptimal specificity of a therapeutic PPI trial and placebo response to proton pump inhibitor⁴⁴, this approach carries the chance of long-term PPI therapy for non-GERD symptoms. While high-quality data interpretation does not

Table 1 Comparison of approach to gastroesophageal reflux disease between India and the Western world. *PPI* proton pump inhibitors, *H2RA* histamine 2 receptor antagonist, *GERD* gastroesophageal reflux disease

Similarities	
Presentation	<ul style="list-style-type: none"> • Common clinical condition • Increasing prevalence • Typical and atypical presentations are both encountered • Obesity is a risk factor • Lifestyle factors contribute • Symptoms do not correlate with endoscopic severity • Functional dyspepsia may coexist • Eosinophilic esophagitis needs exclusion • Achalasia, rumination, and supragastric belching can mimic GERD
Investigation and management	<ul style="list-style-type: none"> • Lifestyle/behavior modifications are first line • H2RA are used for infrequent symptoms • PPI trial is diagnostic and therapeutic • Prokinetics are of limited clinical value • Long-term PPI therapy is appropriate for complicated GERD • Injudicious PPI use should be avoided • Endoscopy for alarm symptoms and PPI non-responders • Ambulatory reflux monitoring can define reflux burden • Antireflux surgery is an alternative for proven GERD
Differences	
Presentation	<ul style="list-style-type: none"> • Less consensus on role of altered lifestyle • Esophagitis is typically low grade • Barrett's esophagus less common • Incidence of esophageal adenocarcinoma is low
Investigation and management	<ul style="list-style-type: none"> • Refractory GERD diagnosed early • Wireless pH monitoring less utilized • Role of manometry not well defined • Barrett's screening not standard • Emerging diagnostic techniques remain experimental • Magnetic sphincter augmentation is not standard • Endoscopic antireflux procedures are evolving

support many of the reported PPI side effects from association studies [46, 58], and the risk-benefit ratio for PPI use favors benefit in proven GERD [59], there remains concern among the public and among some practitioners that PPIs are significantly harmful. Therefore, a step-down approach, reducing PPI dose or transitioning to an H2RA after a period of 8–12 weeks, has clinical value in reducing cost and side effects of therapy [60]. On the contrary, in established GERD, especially with erosive esophagitis or BE, continuous PPI therapy maintains healing of esophagitis [61], while stepping down from PPI therapy risks recurrence of esophagitis and progression of BE. Prokinetic medications have not been demonstrated to provide adjunctive value in the management of GERD symptoms.

Diagnostic evaluation

A pragmatic investigation protocol can augment precision management, typically when symptoms do not respond to initial acid suppressive therapy (persistent symptoms) or when esophageal symptoms in the context of proven GERD persist despite therapy (refractory GERD). The Indian Consensus emphatically agreed that symptoms do not correlate with objective evidence of GERD [1]. The role of esophageal hypersensitivity and functional dyspepsia in driving persistent foregut symptoms influences the approach to the symptomatic patient [62]; three-quarters of the Indian opinion leaders agreed with this. Precise evaluation of refractory esophageal symptoms is critical, as escalation of reflux management will only be effective if targeted toward true refractoriness of symptoms in the setting of proven GERD [57]. While the position statement suggests non-response to optimal PPI therapy over 8 weeks as defining refractory GERD, this definition applies to refractory esophageal symptoms rather than true refractory GERD [57]. A diagnosis of refractory GERD requires documentation of persisting reflux of gastric content into the esophagus despite adequate acid suppression, leading to troublesome symptoms and/or mucosal damage [16]. To this end, understanding what constitutes adequate acid suppressive therapy is crucial [57], as the trigger for further investigation typically consists of lack of response to adequate acid suppression. An investigation protocol can also help rule out GERD, so management can shift to other approaches that may have better value than acid suppression.

Therefore, in patients with persisting symptoms despite acid suppressive therapy, alarm symptoms and prior evidence for conclusive GERD determine how further evaluation is pursued. Confirming appropriate PPI dosing before meals and adoption of lifestyle measures are useful initial steps [50, 63, 64]. Despite the high number needed to treat for symptom improvement [65], temporarily increasing acid suppression to twice a day (before breakfast and supper) is a simple step that may obviate further invasive evaluation. Investigation starts with an upper endoscopy [18] to evaluate for confounding diagnoses or complications of GERD [20], despite the low yield for GERD evidence when performed on acid suppressive therapy [66]. Invasive investigation then progresses esophageal physiologic testing, including ambulatory reflux monitoring and/or esophageal high-resolution manometry (HRM) [16, 20, 67].

When the decision is made for invasive investigation, the practitioner needs to preemptively decide how test results will influence management. Documentation of abnormal reflux metrics may entail escalation of therapy, to potentially include surgical or invasive antireflux therapy depending on local expertise and availability (Fig. 1) [57]. On the contrary, if reflux metrics are in the physiologic range, de-escalation of GERD therapy in favor of symptomatic management of functional or behavioral disorders may be warranted. When reflux metrics are inconclusive, the sum of evidence from multiple

conventional and novel tests is combined with clinical symptomatology and practitioner opinion to determine the contribution of GERD to persisting symptoms [20]. Since functional esophageal symptoms can mimic GERD, and since there is significant overlap between functional esophageal disorders and GERD [68], esophageal physiologic testing is a prerequisite to invasive management, to demonstrate the presence of pathologic reflux burden or evidence of mucosal injury from GERD [16]. Esophageal manometry evaluates for major motor disorders (such as achalasia) mimicking GERD and defines the pathophysiology of GERD in terms of EGJ morphology and esophageal peristaltic performance, which may in turn allow better choice of invasive management options [20, 67].

In patients without prior evidence for GERD, ambulatory reflux monitoring is performed off acid suppression, for the purpose of making an initial diagnosis of GERD, and for decision-making in terms of maintenance, escalation, or discontinuation of antireflux measures [20]. The exact mode of reflux monitoring matters less than performing the test off PPI; therefore, local availability and expertise can determine choice between catheter-based pH, pH impedance, and wireless pH monitoring [16]. However, in patients with “proven GERD” (prior documentation of high-grade reflux esophagitis, BE, and peptic stricture, or prior positive pH monitoring) with persisting symptoms, optimal reflux monitoring consists of pH impedance monitoring on maximal acid suppression. The purpose of testing in this instance is to determine if current management of reflux is inadequate and if ongoing symptoms associate with persisting reflux episodes, both of which indicate a need for further escalation of reflux management to antireflux surgery or other invasive measures [16].

Novel investigative modalities have been introduced to improve diagnostic accuracy and to facilitate precision management of GERD. Utilizing known alterations in mucosal integrity and subsequent changes in mucosal impedance related to chronic reflux, a novel tool that analyzes mucosal impedance in real time is gaining attention [69]. Both narrow band imaging and confocal laser endomicroscopy have been investigated as potential methods for rapid detection of mucosal changes during endoscopy [70, 71]. Given established relationships between esophageal motor abnormalities and reflux burden, the functional lumen imaging probe (FLIP) is being investigated for ruling out esophageal outflow obstruction mimicking reflux, and as an adjunctive tool evaluating for pathophysiologic mechanisms underlying refractory GERD.

Regional bias and availability of resources play a key role in the approach to GERD. Although pH impedance monitoring has advantages in detecting non-acidic reflux events while on therapy [16], interpretation remains cumbersome, and outcome data based on impedance metrics are limited [22]. Catheter-based 24-h pH monitoring is a reasonable fallback, as this is cheaper, with more

widespread availability and easier interpretation. Wireless pH monitoring, routinely utilized in the USA, allows for monitoring up to 96 h, which is useful in patients intolerant of catheters, with infrequent symptoms or with day-to-day variation in acid burden [71]. Yet this is not part of standard practice in India and was felt of limited utilization in the Indian Consensus [1]. There is a growing body of literature suggesting HRM can complement standard diagnostic techniques in predicting GERD [20]. However, the Indian Consensus suggests that there is no role for manometry in their GERD population [1], potentially related to access to HRM. Other newer diagnostic modalities such as mucosal integrity and FLIP are also not routinely available yet in India. It is anticipated that availability and familiarity with these newer modalities will improve over time. Availability of resources is an important driving factor in implementation of guidelines on a regional basis, and the variability between Indian and Western approaches to GERD is a reflection of this fact.

In conclusion, there are more similarities than differences in GERD presentation, evaluation, and management between New Delhi and New York. However, regional differences are important and need to be factored into the management paradigm. Position statements from regional opinion leaders are crucial in providing valuable local flair to international consensus guidelines. However, it is important for the average practitioner to understand that guidelines are just that—a guide to investigation and management that should be interpreted and applied in light of each patient’s unique presentation and within the practitioner’s knowledge and experience. Consequently, improvement in diagnosis, management, and most importantly symptomatic outcome will only result with comprehensive education, availability of contemporary diagnostic and management tools, and guidance from regional opinion leaders, whether GERD is managed in New York or New Delhi.

Compliance with ethical standards

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