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Advances in the physiological assessment and diagnosis of GERD

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Abstract | GERD is a common condition worldwide. Key mechanisms of disease include abnormal oesophagogastric junction structure and function, and impaired oesophageal clearance. A therapeutic trial of acid-suppressive PPI therapy is often the initial management, with endoscopy performed in the setting of alarm symptoms and to exclude other conditions. If symptoms persist and endoscopy does not reveal evidence of GERD, oesophageal function tests are performed, including oesophageal manometry and ambulatory reflux monitoring. However, reflux episodes can be physiological, and some findings on endoscopy and manometry can be encountered in asymptomatic individuals without GERD symptoms. The diagnosis of GERD on the basis of functional oesophageal testing has been previously reported, but no updated expert recommendations on indications and the interpretation of oesophageal function testing in GERD has been made since the Porto consensus over a decade ago. In this Consensus Statement, we aim to describe modern oesophageal physiological tests and their analysis with an emphasis on establishing indications and consensus on interpretation parameters of oesophageal function testing for the evaluation of GERD in clinical practice. This document reflects the collective conclusions of the international GERD working group, incorporating existing data with expert consensus opinion.

GERD consists of troublesome symptoms or mucosal damage resulting from retrograde movement of gastric content through an incompetent oesophagogastric junction (EGJ)[1]. GERD is one of the most common gastrointestinal ailments worldwide; up to 40% of the US population report oesophageal symptoms intermittently and 10–20% have at least weekly symptoms[2,3].

Typical GERD symptoms consist of heartburn and regurgitation, and clinical diagnosis is made on the basis of typical symptoms, supported by symptom response from empiric PPI therapy[4,5]. Alarm symptoms (for example, dysphagia, weight loss, anaemia), atypical presentations (including chest pain, laryngeal symptoms) or lack of response to empiric therapy prompt further evaluation with an upper endoscopy (EGD; oesophagogastroduodenoscopy)[4,6]. If symptoms persist despite empiric therapy, and EGD does not reveal evidence of GERD (oesophagitis, peptic oesophageal stricture, Barrett mucosa), oesophageal function tests are performed, including oesophageal manometry and ambulatory reflux monitoring[7]. However, reflux episodes can be physiological, and some findings on endoscopy (Los Angeles (LA) classification grade A or B reflux oesophagitis[8]) and manometry (hypotensive EGJ, ineffective oesophageal manometry) can be encountered in asymptomatic individuals without GERD symptoms[9]. GERD diagnostic criteria on the basis of oesophageal testing have been previously reported[7,10–12]; however, no updated consensus on indications and interpretation of oesophageal function testing in GERD among experts in the field has been made since the 2004 Porto consensus[13].

Under the auspices of the International Working Group for Disorders of Gastrointestinal Motility and Function (www.idigest.ch), the authors of this manuscript organized a consensus project to describe modern oesophageal physiological tests and their analysis. The aim of this consensus project was to obtain 'a standard of practice' for clinicians and motility laboratories worldwide, and to reorganize and reiterate existing knowledge regarding GERD evaluation, as it has been over a decade since the last consensus of its kind in Porto[13]. Throughout this process, emphasis was focused on establishing indications and agreeing on interpretation

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of oesophageal function testing for the evaluation of GERD in clinical practice. This Consensus Statement reflects the collective clinical conclusions of the international GERD working group evaluating modern GERD testing and interpretation, incorporating existing data with expert consensus opinion. Novel concepts and recommendations developed through this process are shown in BOX 1 and will be further discussed throughout.

Methods

The GERD consensus steering committee (S.R., C.P.G., E.S., A.B.) was appointed by the International Working Group for Disorders of Gastrointestinal Motility and Function. Under the guidance of the steering committee, an international GERD working group performed focused literature searches using search terms pertaining to GERD (for example, "GERD testing", "GERD diagnosis", "ambulatory pH" and "pH-impedance monitoring", "hiatus hernia", "transient lower oesophageal sphincter (LES) relaxation", "oesophageal dysmotility", "oesophageal manometry", "endoscopy", "GERD phenotypes") to identify pertinent statements relating to oesophageal pathophysiology and oesophageal function testing in the context of GERD. At consensus meetings attended by international GERD experts held in conjunction with international conferences (United European Gastroenterology week 2015–2017, Digestive Disease Week 2015–2016, Ascona II 2015), these statements were extensively discussed and debated. Consensus was achieved through careful evaluation using the GRADE concept[14] to define the quality of the supporting evidence based on study design, study limitations, consistency, directness, precision, publication bias, other modifying factors and expert agreement when guidelines lacked supporting evidence.

Box 1 | **Key advances in the clinical approach to GERD**

- The concept of proven GERD, with prior endoscopic or physiological evidence of disease, versus unproven GERD is utilized to direct which oesophageal reflux monitoring study to use and whether it should be performed on or off acid suppressive therapy
- Consensus definitions of thresholds for pH and pH-impedance monitoring have been made in defining physiological and pathophysiological reflux measurements, including an inconclusive 'grey area' that requires further evidence to confirm a diagnosis of GERD
- Acid exposure time is physiological when <4% and pathological when >6%; values in between are considered borderline, requiring additional clinical or physiological evidence to confirm or refute a GERD diagnosis
- When the diagnosis is inconclusive on reflux monitoring alone, the use of additional features are suggested, including histology, new pH-impedance metrics and high-resolution manometry
- A new classification of oesophageal contractility and oesophagogastric junction motor findings in GERD is made, incorporating data obtained by high-resolution manometry

Mechanisms of gastro-oesophageal reflux

Oesophagogastric junction barrier. An ineffective EGJ barrier is consistently present in GERD (FIG. 1), often combined with morphological abnormality (hiatus hernia). Transient lower oesophageal sphincter relaxation (TLESR) is a physiological response to gastric distension, and excessive reflux during TLESRs is the most common EGJ event seen in patients with GERD[15]. Modern high-resolution manometry (HRM) criteria for TLESRs include profound EGJ relaxation of >10 s in the absence of swallowing, with inhibition of crural diaphragm contraction[16]. TLESRs are not routinely evaluated on oesophageal HRM, although they do affect oesophageal reflux burden. By contrast, motor deficiency and abnormal morphology of the EGJ barrier are readily identified on HRM.

An intact EGJ barrier consists of superimposed LES and crural diaphragm, with adequate resting tone preventing retrograde migration of gastric content at rest (FIG. 1). EGJ morphology is characterized into three morphological subtypes: subtype 1 (normal), subtype 2 (<3 cm separation between LES and crural diaphragm) and subtype 3 (≥3 cm separation between LES and crural diaphragm)[17]. The intrinsic LES can independently have a low resting tone, with values <5 mmHg during the end expiratory phase being considered abnormal[12]. Inspiratory crural diaphragm augmentation provides adjunctive EGJ barrier function when intrathoracic pressures are at their lowest[18,19]; this phenomenon is an important element not well-assessed by basal and end expiratory LES pressure measurements. The EGJ contractile integral might overcome these drawbacks by combining EGJ anatomy, basal tone and variation with respiration into a single metric, calculated using an algorithm similar to the distal contractile integral that takes into account the length and vigour of the EGJ resting barrier function and corrected for respiratory variation[20,21]. Normative EGJ contractile integral values have been described and available data suggest reflux burden might be abnormal in the setting of a low EGJ contractile integral[21–23]. Thus, an abnormal EGJ barrier can be hypotensive (with reduced resting tone that can be overcome by increased intra-abdominal pressure), disrupted with separation of the two components of the EGJ barrier (hiatus hernia) or both. In the presence of a hiatus hernia, the resting tone of the intrinsic LES is typically hypotensive, with oesophageal reflux burden higher than with either abnormality alone[24]. Consequently, these two EGJ abnormalities can coexist and both can contribute to abnormal reflux burden.

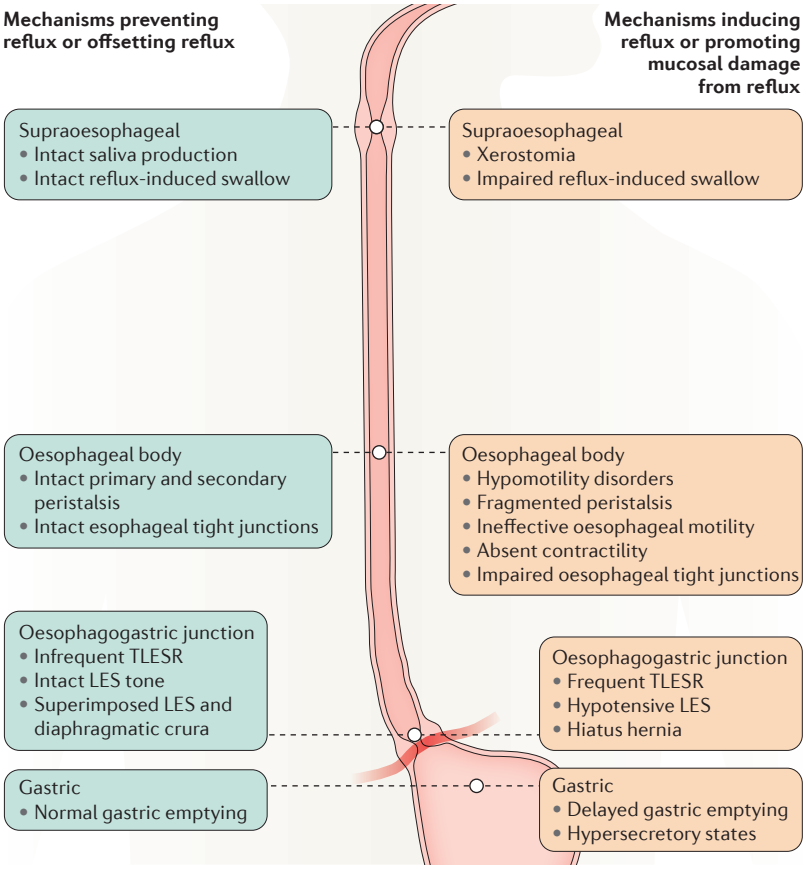

Figure 1 | **Pathophysiology of GERD at the oesophagogastric junction and oesophageal body.** The left side describes mechanisms preventing or off-setting gastro-oesophageal reflux, whereas the right side elaborates mechanisms inducing gastro-oesophageal reflux or promoting mucosal damage from reflux. LES, lower oesophageal sphincter; TLESR, transient lower oesophageal sphincter relaxation.

Oesophageal hypomotility. When a reflux episode occurs, the refluxate is cleared by a combination of a secondary peristaltic contraction and a primary post-reflux swallow-induced peristaltic contraction that also brings saliva to neutralize oesophageal mucosal acidification[25]. In many patients with GERD, oesophageal motor function is intact and normal[26]; however, hypomotility can contribute to delayed oesophageal clearance and increases the likelihood of oesophagitis[27–29]. The spectrum of hypomotility consists of fragmented peristalsis, ineffective oesophageal motility and absent contractility, with increased prevalence of abnormal oesophageal bolus clearance towards the high end of this spectrum[30–32].

Refluxate. The acid pocket is a supernatant layer of gastric acid overlying an ingested meal immediately below the EGJ. In health, the transition from an acid to alkaline milieu occurs at the EGJ in the post-prandial period[33]. However, when the EGJ barrier is weak or disrupted, for example in presence of hiatus hernia, the acid pocket can migrate into the distal oesophagus, leading to pathological acid in the distal oesophagus[34]. Delayed gastric emptying and acid hypersecretory states, such as in gastrin-secreting tumours (gastrinomas), are additional downstream factors that contribute to oesophageal reflux burden[35]. Acid and other components of the refluxate (pepsin, bile acid) can participate in mucosal damage and in complications including Barrett metaplasia[36].

Finally, the degree of proximal migration of the refluxate and differences in oesophageal perception of reflux (sensitivity) between individuals can contribute to symptom reporting in GERD[37]. Symptoms identical to typical GERD can be reported with reflux hypersensitivity and functional heartburn, in which oesophageal reflux burden is physiological; both can overlap with true GERD when symptoms persist despite reflux burden being rendered physiological with acid-suppressive therapy[38].

Oesophageal manometry in GERD

The pathophysiology of GERD does not have a direct implication on initial GERD management, as treatment consists of acid suppression. However, if GERD symptoms persist despite empiric therapy and endoscopy is normal, further oesophageal testing is recommended (BOX 2). Manometry is commonly performed for positioning of pH or pH-impedance catheters. When symptoms persist, manometry is also performed to exclude achalasia and alternate disorders that can mimic GERD, such as rumination, systemic sclerosis and supragastric belching[26,39]. Consequently, understanding motor mechanisms of GERD and identifying conditions mimicking GERD complement information obtained from ambulatory oesophageal reflux monitoring in planning management (TABLE 1). However, the Chicago Classification of oesophageal motor disorders targets abnormal bolus transit with symptomatic dysphagia and chest pain, but was not designed to assess motor function in the context of GERD[40]. Thus, the proposed classification, devised by this international GERD working group and detailed in the following subsections, represents an advance to previous classifications by attempting to provide structure in analysing HRM studies performed in the context of GERD[40].

Most metrics (LES basal pressure, integrated relaxation pressure, distal contractile integral, hiatus hernia size) utilized in reporting oesophageal motor function in GERD are readily obtained from oesophageal HRM (FIG. 2) using a standard protocol of ten 5 ml water swallows in the supine position. Furthermore, when oesophageal peristaltic performance is abnormal, oesophageal body contraction reserve (potential for augmentation of oesophageal body contraction when ineffective oesophageal motility is found on routine water swallows) can be determined using provocative testing. The simplest provocative tests consist of either a series of five 2 ml water swallows in rapid succession, termed multiple rapid swallows[41,42], or free drinking of 100–150 ml of water from a cup, termed rapid drink challenge[43,44]. During the series of swallows, inhibition of oesophageal body contraction and relaxation of the LES occurs. Following the final swallow of the sequence, there is augmented oesophageal body contraction and re-establishment of LES tone[41,42]. Augmentation of oesophageal body contraction is measured as the ratio between

Box 2 | **Indications for oesophageal function testing in GERD**

Indications for ambulatory reflux monitoring

- Typical symptoms (heartburn, regurgitation) persisting despite PPI therapy
- Atypical symptoms (chest pain, cough, laryngeal symptoms), to confirm or exclude GERD
- Documentation of abnormal oesophageal reflux burden before invasive antireflux procedures and surgery
- Diagnosis of functional heartburn and reflux hypersensitivity (by exclusion of pathological AET)
- Diagnosis of supragastric belching (pH impedance) and rumination syndrome (in conjunction with manometry)

Emerging indications

- Monitoring of reflux burden following invasive reflux procedures and surgery
- Monitoring of reflux burden following ablation of the LES in achalasia

Indications for manometry in GERD

- Localization of the LES for appropriate placement of pH and pH-impedance catheters
- Exclusion of major motor disorders, especially achalasia
- Assessment of oesophageal peristaltic performance before invasive antireflux procedures and surgery
- Diagnosis of rumination syndrome and supragastric belching (in conjunction with pH impedance)
- Evaluation of post-fundoplication dysphagia
- Diagnosis of functional oesophageal disorders by exclusion of major motor disorders

Emerging indications

- Assessment of morphology and integrity of the oesophagogastric junction
- Measurement of hiatus hernia size
- Assessment of oesophageal peristaltic performance before bariatric procedures

AET, acid exposure time; LES, lower oesophageal sphincter

distal contractile integral (DCI) following multiple rapid swallows and the mean DCI during standard wet swallows. Contraction reserve indicates a DCI ratio >1, and enables phenotyping of oesophageal body peristalsis with implications on management outcome[42,45]. Absence of contraction reserve is associated with an increased likelihood of transit symptoms (dysphagia) following a 360° fundoplication[42].

Evaluation and reporting of oesophageal motor function in GERD can be achieved through three hierarchical steps, as outlined in the following subsections. The first two steps can reveal abnormalities that can be independent of each other; however, the coexistence of abnormalities might predict an increased likelihood of abnormal oesophageal reflux burden. The final step only applies when oesophageal body motor function is abnormal and as an exploratory tool that might have implications on management outcome.

Integrity of the oesophagogastric junction barrier. EGJ hypomotility is defined as low EGJ resting tone, with end expiratory LES pressure <5 mmHg (REF. 12), or EGJ contractile integral <39–47 mmHg per cm (REFS 20–22). EGJ morphology is based on the relationship between the intrinsic LES and crural diaphragm, and is described as one of the three EGJ subtypes described in the previous section. When the EGJ barrier is intact, the EGJ resting tone is normal and the LES and crural diaphragm are superimposed (EGJ morphology type 1). A hypotensive EGJ can sometimes occur as an isolated abnormality; however, this finding often coexists with a hiatus hernia (EGJ morphology types 2 or 3)[17].

Oesophageal body motor function. Intact or normal oesophageal body motility consists of <50% of swallows with DCI <450 mmHg·cm·s (REF. 40). Fragmented peristalsis is defined by the presence of ≥50% fragmented swallows, whereby DCI is >450 mmHg·cm·s but there are ≥5 cm breaks in the 20 mmHg peristaltic contour[40]. Ineffective oesophageal motility consists of ≥50% ineffective sequences, in which DCI is <450 mmHg·cm·s (REF. 40). Absent contractility describes uniformly failed sequences, in which DCI is <100 mmHg·cm·s (REF. 40).

Oesophageal body contraction reserve. This metric is evaluated when oesophageal body motor function is abnormal. Contraction reserve is present when multiple rapid swallow DCI is higher than the mean wet swallow DCI. For example, the ratio between multiple rapid swallow DCI and wet swallow DCI is >1 (REF. 42).

Ambulatory reflux monitoring Proven versus unproven GERD. Ambulatory reflux monitoring is performed to document oesophageal reflux burden or to define the relationship between symptom events and reflux episodes. The most common settings consist of persisting oesophageal symptoms despite seemingly adequate acid-suppressive therapy, such as a failed PPI test or atypical symptoms (chest pain, cough, laryngeal symptoms) that might not directly implicate GERD but could improve with GERD therapy if pathological reflux is present[4,5] (FIG. 3). In the typical clinical scenario, ambulatory reflux monitoring has either rule-in or rule-out value in defining abnormal oesophageal reflux burden[46]. The concepts of unproven GERD and proven GERD, deliberated extensively and defined here precisely during this consensus process, determine how reflux monitoring is performed. In the absence of prior evidence of reflux (unproven GERD; with no prior LA classification grade C or D oesophagitis, peptic stricture or Barrett mucosa on endoscopy, or no prior positive ambulatory reflux study), or before antireflux surgery (ARS; for example, Nissen or Toupet fundoplication), testing is performed off anti-secretory therapy for 7–10 days[47]. When irrefutable evidence of GERD exists (proven GERD; EGD evidence of LA classification grade C or D oesophagitis, peptic stricture, long-segment Barrett mucosa or prior abnormal ambulatory reflux monitoring), testing can be performed on anti-secretory therapy, in which the objective is to determine if ongoing symptoms can be explained by abnormal oesophageal reflux burden or linked to reflux episodes. In this setting, pH testing alone is insufficient in describing weakly acidic reflux episodes that predominate in patients on PPI therapy, therefore, pH-impedance testing is used[48]. When reflux monitoring is repeated after ARS or other invasive reflux therapy, the same testing method used before intervention is performed, typically off anti-secretory therapy. If suspicion of GERD is strong in the setting of negative 24 h reflux monitoring, repeated and prolonged

monitoring using a wireless pH probe can be considered, as day-to-day variation in oesophageal reflux burden has been documented and some patients struggle to eat and behave normally with an oesophageal catheter in place[49]. Repeat testing in this context could improve diagnostic yield and the finding of abnormal reflux burden can affect management direction[49,50].

As typical reflux symptoms are initially managed with an empiric PPI trial, persisting symptoms despite PPI therapy can be an indication for ambulatory reflux monitoring (FIG. 3). However, the PPI trial is not perfect, with a specificity of only 50–60% despite sensitivity of ~80% in predicting erosive oesophagitis or an abnormal pH study[51,52]. Investigation of persisting reflux symptoms, or alarm symptoms, starts with an EGD with biopsies to exclude alternative mucosal processes, such as infectious oesophagitis or eosinophilic oesophagitis[53]. Persisting symptoms, both typical and atypical, necessitate ambulatory reflux monitoring to determine if antireflux therapy is indicated; the more atypical the symptoms, the greater the need for ambulatory reflux monitoring.

Reflux metrics. Oesophageal acid exposure time (AET) is the most commonly used metric in defining abnormal oesophageal reflux burden. AET can be extracted from both pH and pH-impedance studies (FIG. 4) and is calculated as the percentage of time that pH is <4.0 in the distal oesophagus (5 cm above the LES) for the duration of the ambulatory study[7,10]. AET can be separately calculated for upright and supine periods. Pathological supine AET can implicate a disrupted EGJ barrier, as TLESRs are generally suppressed during sleep[54]. Symptom–reflux association is an essential part of interpretation. This process requires the patient to report symptoms during the ambulatory study, typically using an event monitor button on the reflux monitoring device worn by the patient[55]. Concurrent reflux episodes are identified by reflux software using pH drops below 4.0 or impedance-detected retrograde movement of gastric content (FIG. 4). A symptom event is considered associated with a reflux episode if the symptom occurs within 2 min following the reflux episode[7].

Although AET and symptom reflux association are the two main metrics used in interpreting ambulatory reflux monitoring studies, additional metrics can be extracted, especially when pH-impedance testing is used. Number of reflux episodes is often reported, and impedance-detected reflux episodes are more reliable than those detected based on decreases in pH alone[56]. Proximal oesophageal and pharyngeal reflux monitoring using pH or impedance sensors is possible; however, this approach has limited value in directing anti-reflux therapy as symptom outcome cannot be predicted based on these metrics[57,58]. Baseline mucosal impedance, especially when measured at night when swallow-related artefacts are at a minimum (MNBI; mean nocturnal baseline impedance), correlates inversely with AET and can be a marker of abnormal mucosal integrity[59,60]. The post-reflux swallow-induced peristaltic wave (PSPW) is an antegrade impedance-detected bolus propagation reaching all distal impedance monitoring sites within 30 s of a reflux event, and is an assessment of clearance of refluxate that can be measured in patients studied on or off therapy. The PSPW index identifies the proportion of reflux events followed by PSPW compared with all other reflux events, and can be lower in erosive and nonerosive GERD compared with healthy individuals as controls[59]. Furthermore, this index might assist in distinguishing hypersensitive oesophagus from functional heartburn[61,62].

Interpretation of reflux monitoring

Data acquisition. Catheter-based ambulatory reflux monitoring (pH or pH-impedance studies) is performed over a 24 h period, with the distal oesophageal pH sensor positioned 5 cm proximal to the manometrically

Table 1 | **Conditions mimicking GERD**

Condition	Manifestations	Evaluation	Characteristic findings on oesophageal function tests
Achalasia	Dysphagia, regurgitation of ingested foods, chest-pain, weight loss	Clinical history, conventional manometry, HRM, HRIM, barium radiographs	Oesophageal outflow obstruction, with or without retained oesophageal body peristalsis
Rumination syndrome	Post-prandial regurgitation of gastric content as a learned behaviour	Clinical history, conventional manometry, HRM, HRIM, pH-impedance	Simultaneous increase in pressure in intra-abdominal and thoracic cavity ('r' wave)
Supragastric and gastric belching	Air swallowing, followed by belching of air	Clinical history, HRIM, pH-impedance	Antegrade air movement followed by retrograde belching of air
Infectious oesophagitis	Dysphagia	Endoscopy with biopsies	No characteristic motor finding
Eosinophilic oesophagitis	Abnormal oesophageal wall compliance or presence of strictures with consequent dysphagia, bolus impaction and regurgitation	Clinical history, endoscopy with biopsies	No characteristic motor finding
Oesophageal diverticula	Post-prandial regurgitation of ingested foods	Clinical history, endoscopy, barium radiographs	Spastic features distal to diverticula, oesophageal outflow obstruction
Functional oesophageal syndromes	Any oesophageal symptom, including heartburn, chest pain or dysphagia	Clinical history, endoscopy, barium radiographs, conventional manometry, HRM, HRIM, pH-impedance	Normal oesophageal function tests, or minor motor disorders on manometry

HRIM, high-resolution impedance manometry; HRM, high-resolution manometry.

measured LES. Wireless pH probes are typically positioned 6 cm proximal to the squamocolumnar junction during EGD. These single sensor probes can record and transmit distal oesophageal pH data for up to 96 h and are better tolerated than ambulatory catheter-based testing[46]. Catheter or probe placement is performed after an overnight fast and after withholding antisecretory therapy for at least 7 days when testing off PPI is performed. Patients are recommended to maintain normal activities and meals, and keep a diary of meals, symptoms, and recumbency periods[7,10].

Analysis of pH data. The key metric extracted from any pH or pH-impedance study is the AET, which requires at least 16 h of recording. Meal times are excluded and the study is scanned visually to identify artefacts, catheter displacement or wireless probe dislodgement that could affect AET calculations. Total AET is considered physiological when <4%, as determined from normative studies (TABLE 2), and pathological when >6%, whereas values in between are borderline and require additional clinical or physiological evidence to confirm GERD[63–70]. Total, upright and supine AET are separately calculated and reported. When a dual-probe pH catheter is used, proximal oesophageal AET can also be reported (FIG. 4b,c). With wireless pH testing, averaged AET and AET for each day of pH recording are separately available. Specificity increases with averaged AET, whereas sensitivity is increased with AET from the worst day during the study. AET is marginally higher with the wireless probe compared with catheter-based pH studies, but similar thresholds can be used for both modes of reflux monitoring[49,71,72]. AET is considered more statistically valid and reproducible than the composite DeMeester score that takes upright, supine and total AET, longest reflux episode, reflux episodes >5 min and the total number of reflux episodes into account[73].

Symptom reflux association. Episodic symptoms with finite onset and offset can be subject to evaluation of symptom reflux association (FIG. 4d), whereas continuous symptoms cannot be assessed by this approach. The dominant or most bothersome symptom is utilized for primary evaluation, secondary symptoms can also be evaluated. A cough detector can count and time cough events; this objective can also be achieved with ambulatory manometry. A simple ratio of associated symptoms to all symptoms defines the symptom index, which is abnormal if >50%[74]. In addition, the number of symptoms should be reported for relevance, as the symptom index can be based on one event only. Symptom association probability (SAP) takes into account 2 min periods with and without reflux episodes and symptom events, and applies a statistical test (Fisher's exact test) on a two-by-two table generated with this data[55]. A *P* value <0.05 (or SAP >95%) corresponds to a <5% chance that symptoms and reflux episodes could have co-occurred just by chance[55]. A similar conclusion can be reached using the Ghillebert probability estimate, which utilizes post-hoc statistical modelling from parameters routinely collected during a pH study to define symptom reflux association[75]. The yield and diagnostic value of symptom reflux association is highest when many symptoms are recorded, with the patient recording the symptom promptly upon occurrence[76]. Multiple symptoms with the 2-min window are counted as a single symptom. Substantial day-to-day variability in reflux episodes and in symptom occurrence does occur, but the results of symptom reflux association are reproducible if sufficient symptom events are observed during the study[77]. Recording of symptoms represents the weakest element in symptom reflux association testing, as incomplete or delayed symptom recording by the patient can render this metric negative and of limited clinical value. Thus, careful instruction and explanation to the patient is essential for success. Nevertheless, when positive,

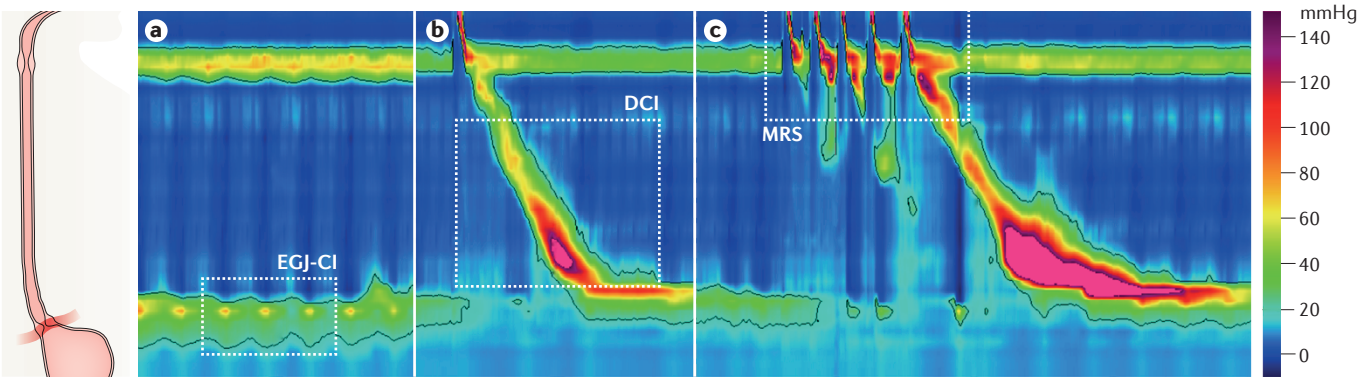

Figure 2 | **Metrics from oesophageal high-resolution manometry used in the characterization of motor function in GERD. a** | Basal and end-expiratory resting pressures are obtained during a period of quiet rest. The oesophagogastric junction contractile integral (EGJ-CI) assesses vigour of the EGJ barrier, taking into account the length and amplitude of pressure of the EGJ above the gastric baseline, corrected for respiration. EGJ morphology is assessed by determining the relationship between the intrinsic lower esophageal sphincter (LES) and the crural diaphragm. **b** | The vigour of oesophageal smooth muscle contraction is assessed using the distal contractile integral (DCI), a measure of the amplitude, length and duration of smooth muscle contraction, normally >450 mmHg·cm·s. DCI <450 mmHg·cm·s indicates ineffective peristalsis, whereas DCI <100 mmHg·cm·s indicates failed peristalsis. If DCI is normal but there is a >5 cm break in peristaltic integrity, the sequence is designated fragmented. **c** | Response to multiple rapid swallows (MRS) consists of an augmented contraction sequence following inhibition of peristalsis during the repetitive swallows. Contraction reserve indicates that the DCI of contraction following MRS is higher than the mean DCI from test swallows (ratio >1).

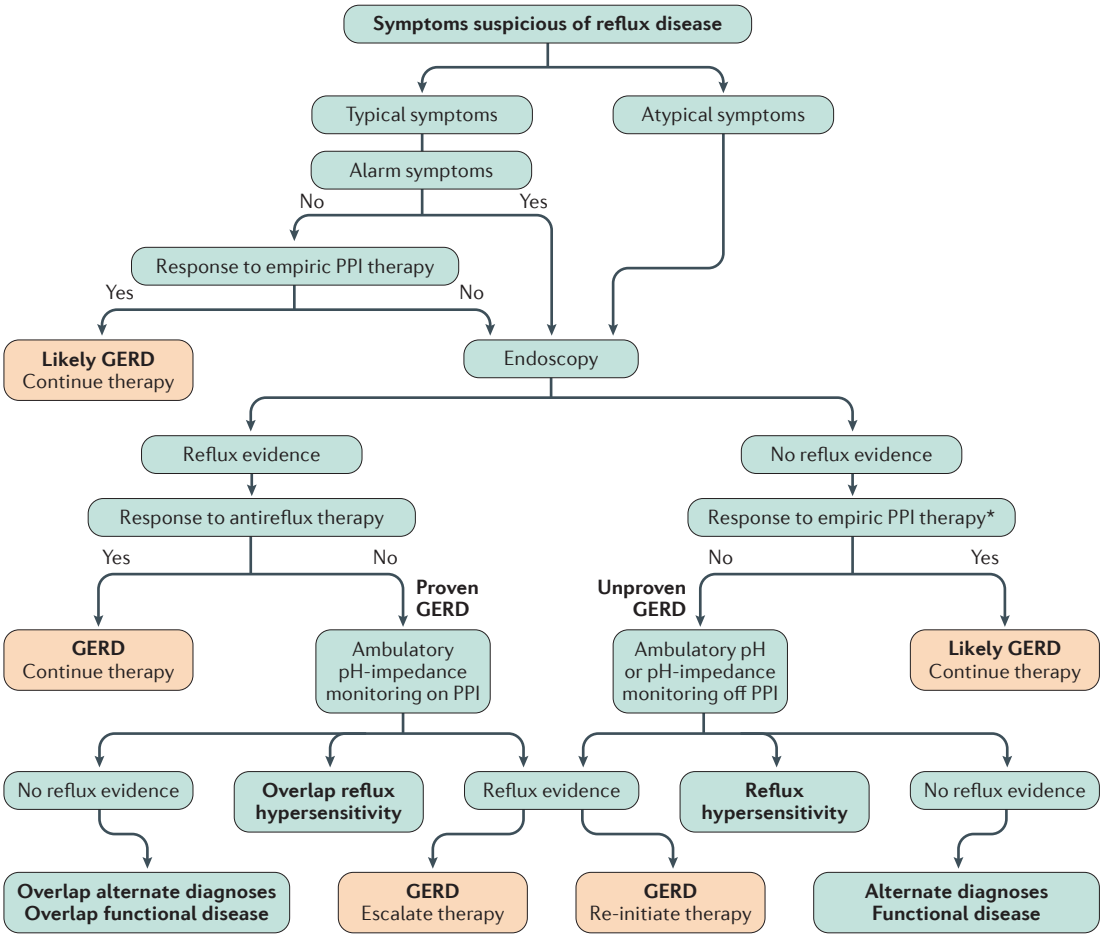

Figure 3 | **Algorithm from working group describing evaluation of oesophageal symptoms suspected to be of reflux aetiology.** Typical reflux symptoms (heartburn, acid regurgitation) are initially treated with empiric acid suppression in the absence of alarm symptoms (dysphagia, anaemia, weight loss). Endoscopy (with oesophageal biopsy sample to evaluate eosinophilic oesophagitis) is performed if alarm symptoms are present, if symptoms do not respond to empiric acid suppression or if presentation is atypical. If endoscopy is negative, an empiric trial of anti-secretory therapy might be indicated, especially with typical symptoms. Los Angeles (LA) classification grade A or B oesophagitis might be encountered in asymptomatic individuals; ambulatory reflux monitoring will be needed if antireflux surgery is planned. With persisting symptoms without clear explanation, ambulatory reflux monitoring is indicated, in the form of either pH or pH-impedance monitoring performed off acid suppression (unproven GERD). Ambulatory reflux monitoring might also be performed in patients with proven GERD (prior LA classification grade C or D oesophagitis, Barrett mucosa, peptic stricture or reflux evidence on prior ambulatory reflux monitoring) if symptoms persist despite antireflux therapy, whereby the intent is to identify persisting reflux evidence, reflux hypersensitivity or absence of reflux evidence. *If not attempted previously.

symptom reflux association can augment the evidence that clinically relevant reflux is present and can define reflux hypersensitivity. Evidence for symptom reflux association is considered to be sound when both SAP and the symptom index are positive[78–80].

Analysis of impedance data. Impedance monitoring was initially believed to provide improved accuracy of reflux evidence, but impedance-based parameters have generally not been predictive of reflux treatment outcomes[81,82]. Although infrequent reflux episodes (<40) could indicate physiological reflux, there is variability in the association of reflux episodes with oesophageal reflux burden[83–88]. High numbers of episodes (>80) could suggest pathological reflux burden, whereas borderline values (40–80) require alternate reflux evidence. By contrast, MNBI could provide complementary longitudinal evidence of oesophageal mucosal damage from reflux exposure. Normative MNBI thresholds have been defined (2,292 Ω), but low values are seen in oesophageal motility disorders with impaired clearance and in abnormal oesophageal mucosa (eosinophilic oesophagitis, Barrett mucosa), which can confound clinical utility[59,89]. Nevertheless, erosive and nonerosive GERD are both associated with lower MNBI values than healthy individuals as controls and patients with functional heartburn[90]. Low MNBI values have also been associated with improved medical and surgical outcome, suggesting relevance in GERD management[60,91]. MNBI could, therefore, represent a complementary or adjunctive metric, available in all settings in which pH-impedance monitoring is performed.

GERD phenotypes. The metrics described earlier have highest value in predicting reflux outcome when testing is performed off PPI therapy in unproven GERD[81,82,92]. Phenotypes with pathological reflux burden on ambulatory reflux monitoring, with or without symptom association, predict the highest likelihood of symptom improvement from antireflux therapy[81,93]. However, thresholds defining pathological from physiological reflux burden are not precise, and a 'grey area' exists, for example, in borderline reflux burden or inconsistent symptom index and SAP, in which the clinical presentation and alternate reflux evidence could complement ambulatory reflux monitoring findings. Symptomatic phenotypes with physiological oesophageal reflux burden can implicate a functional basis for symptoms, whereby symptom improvement is suboptimal with antireflux therapy[38,93]. Within these phenotypes, reflux hypersensitivity consists of symptom–reflux association in the setting of physiological reflux burden, whereas functional heartburn or functional chest pain implies a normal ambulatory reflux monitoring study with negative symptom reflux association[38].

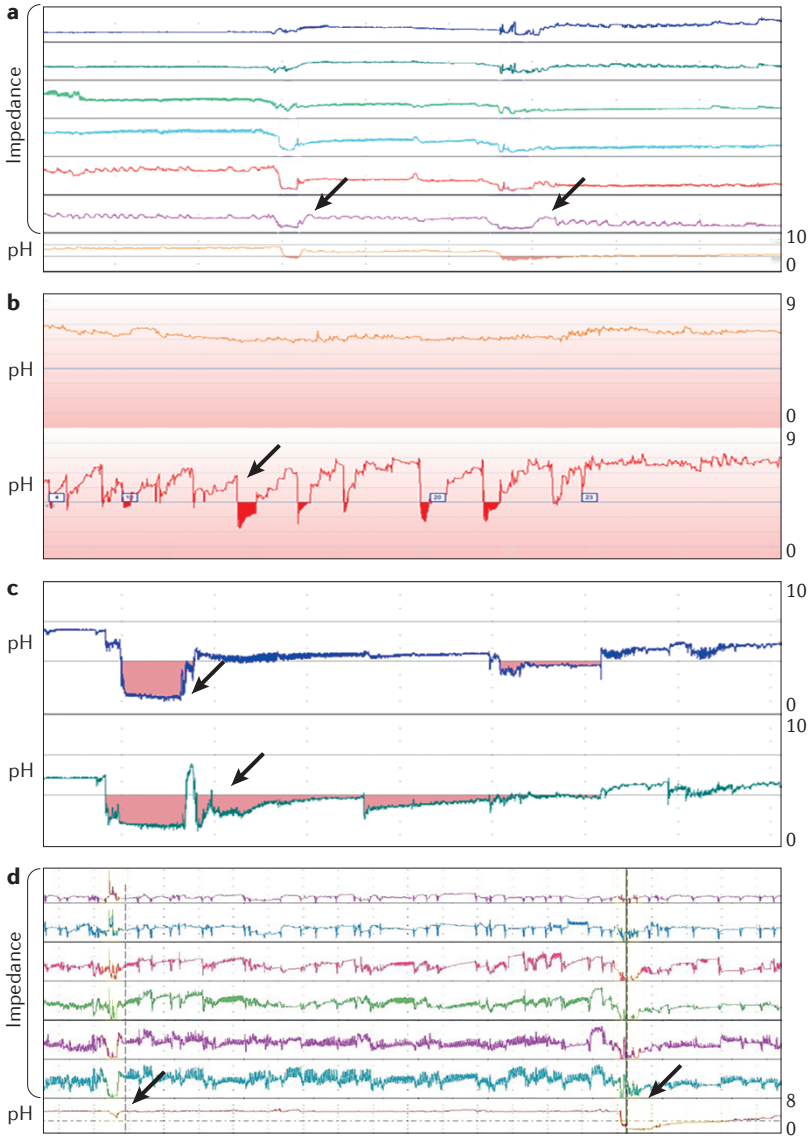

Figure 4 | **Examples of reflux episodes on pH and pH-impedance monitoring.** In all instances, arrows point to reflux episodes. **a** | Acid reflux episodes on pH-impedance monitoring. The pH electrode is positioned 5 cm above the lower esophageal sphincter (LES), and the impedance electrodes at 3 cm, 5 cm, 9 cm, 11 cm, 15 cm and 17 cm above the LES, stacked with the most proximal electrode at the top. Note the abrupt drop in the tracing designated pH, and drop in impedance recordings (arrows). **b** | Distal oesophageal acid reflux episodes on dual-channel pH monitoring, with pH electrodes 15 cm apart, and the distal electrode 5 cm above the LES. Note the drop in pH (arrow) limited to the bottom (distal) tracing only. **c** | Prolonged reflux events with delayed clearance in both distal and proximal channels on dual-channel pH monitoring. Note the pH drop in both distal and proximal tracings (arrows), and persistent low pH following the drop, especially in the bottom (distal) tracing. **d** | Weakly acidic and acidic reflux episodes associated with symptom events (symptoms occurring within 2 min of reflux episodes) on pH-impedance monitoring. The first reflux episode consists of drops in impedance recordings without a prominent drop in pH (arrow), indicating that this is a weakly acidic reflux episode. The second episode consists of drops in both pH and impedance (arrow), indicating that this is an acid reflux episode. Vertical lines indicate when the patient reported symptoms.

Monitoring using pH impedance is also used in proven GERD if symptoms persist, when testing is performed on maximal antisecretory therapy. In these instances, similar AET thresholds can be utilized and the yield of abnormal oesophageal acid burden is expected to be low (typically <1%)[94]. Management decisions will, therefore, need to be based on symptom–reflux association and number of reflux events. Utilizing these parameters, the possible phenotypes prompting escalation of antireflux therapy are as follows (FIG. 3): inadequate control of oesophageal acid burden with antisecretory therapy; persisting symptoms associated with impedance-detected reflux episodes; and abnormally high impedance-detected reflux episodes. By contrast, the following phenotypes could indicate adequate acid control or alternate mechanisms for symptom generation: normal (physiological) oesophageal acid burden; lack of association between persisting symptoms and reflux episodes; and low impedance-detected reflux episodes. Borderline reflux burden could also be encountered in proven GERD with similar implications as in unproven GERD. Additionally, reflux hypersensitivity or functional symptoms could overlap with true GERD. Under all these circumstances, clinical presentation and evidence from other tests for GERD evaluation will need to be combined with results from ambulatory reflux monitoring in planning management.

Other tests for evaluation of GERD

Several questionnaires with varying characteristics have been developed for the assessment of GERD[95]. A few of these have some diagnostic utility and two have been validated in multiple languages: the Reflux Disease Questionnaire (RDQ) and the GERDQ[95–97]. However, both have shown only modest accuracy (~65–70%) for symptom-based diagnosis of GERD and, therefore, cannot be recommended as stand-alone diagnostic instruments[96,97].

Endoscopy has high specificity but very low sensitivity for GERD diagnosis, as oesophageal mucosa is normal in up to 70% of patients with symptomatic GERD[98,99]. When performed following recent or current antisecretory therapy, the probability of a normal assessment increases to 90%[100]. Thus, endoscopy has very low

Table 2 | **Normative thresholds from pH and pH-impedance studies**

Reflux monitoring equipment	Number of healthy controls	Normative thresholds		Refs
		% total time with pH <4.0	Number of impedance-detected reflux episodes per 24 h	
Catheter-based pH monitoring				
Vitale *et al.*, 1984	22	7.2%	NA	63
Schlindbeck *et al.*, 1987	42	7.0%	NA	64
Johnsson *et al.*, 1987	20	3.4%	NA	65
Mattioli *et al.*, 1989	20	5.0%	NA	66
Smout *et al.*, 1989	32	• <45yrs 5.0% • >45yrs 12.0%	NA	67
Masclee *et al.*, 1990	27	4.0%	NA	68
Richter *et al.*, 1992	110	5.8%	NA	69
Kasapidis *et al.*, 1993	18	3.9%	NA	70
Wireless pH monitoring				
Pandolfino *et al.*, 2003	39	5.3%	NA	49
Wenner *et al.*, 2005	48	4.4%	NA	72
Ayazi *et al.*, 2009	50	4.9%	NA	71
pH-impedance off anti-secretory therapy				
Shay *et al.*, 2004	60	6.3%	73	83
Zerbib *et al.*, 2005	62	5.0%	75	84
Tutuian R *et al.* 2006	20	NA	42	85
Savarino *et al.*, 2008	48	4.2%	54	86
Zerbib *et al.*, 2013	46	5.8%	53	87
Kawamura *et al.*, 2016	42	3.3%	85	88
pH-impedance on anti-secretory therapy				
Tutuian R *et al.* 2006	20	NA	22	85
Zerbib *et al.*, 2013	46	0.4%	57	87

Thresholds are expressed as the 95th percentile of normal values. NA, not available

sensitivity for initial GERD diagnosis, and is appropriate only in the presence of alarm symptoms, such as dysphagia or unintentional weight loss, multiple risk factors for Barrett oesophagus (>50 years of age, male sex, prolonged reflux symptoms, obesity) or failure to respond to appropriate antisecretory therapy[6]. Supplemental endoscopic tools such as narrow-band imaging and confocal laser endomicroscopy provide limited additional benefit in identifying mucosal damage consistent with reflux. Their use remains restricted to research given intrinsic limitations such as high costs, time-consuming procedures and weak interobserver and intraobserver agreement. Furthermore, there is higher clinical value with reflux monitoring than these newer tools[101]. Novel endoscopic probes for measurement of oesophageal mucosal impedance have been introduced, providing basal mucosal impedance estimates similar to that obtained from ambulatory pH-impedance monitoring[102–105]. These tools have shown promise in distinguishing reflux disease from functional oesophageal disorders and in monitoring treatment response. Future studies will determine the true potential of these methods as diagnostic tools[106].

Oesophageal biopsies evaluating histological changes potentially related to reflux, such as dilated intercellular spaces, basal cell hyperplasia and papillary elongation, have shown moderate to good sensitivity and specificity in identifying GERD[107–110]. When findings are considered collectively as evidence of microscopic oesophagitis, particularly when combined into a global severity score, distinction of erosive oesophagitis and nonerosive reflux disease from functional heartburn and healthy individuals is possible with good accuracy[111,112]. Furthermore, some studies suggest usefulness of histological findings in monitoring response to medical and surgical therapies[112,113]. Conversely, there are several drawbacks, mainly related to limited specificity and interobserver and/or intraobserver agreement between pathologists[114]. These restrictions limit the usefulness of histological assessment in current clinical practice, although efforts are ongoing to resolve these limitations[114].

The use of barium radiography in diagnosing GERD is not recommended. Data comparing radiographic diagnosis of GERD with that from reflux testing demonstrate that radiographic findings do not correlate with the prevalence or extent of reflux seen on ambulatory pH-impedance monitoring[115]. Thus, barium radiography alone cannot be used to diagnose GERD, although radiography can be accurate and useful in defining EGJ anatomy.

The use of impedance planimetry to measure cross-sectional area and distensibility at the EGJ (endoluminal functional lumen imaging probe or endo-FLIP) has shown no demonstrable value in the diagnostic work-up of GERD, although clinical data are scant[116,117]. Similarly, not enough evidence currently exists to recommend the clinical use of salivary pepsin in the diagnosis of GERD.

Oesophageal function testing implications

GERD phenotypes can be defined on the basis of clinical assessment, endoscopy and oesophageal function testing. The best use of GERD phenotypes lies in predicting outcomes from management, thereby enabling practitioners to choose the most ideal management options to maximize therapeutic outcome. In this regard, symptoms and PPI response do not adequately phenotype GERD into reliable therapeutic categories. Limited research is available describing prediction of therapy outcomes on the basis of presentation, morphology of the EGJ and oesophageal motor function.

Using EGD findings, GERD can be phenotyped into erosive and nonerosive disease, with clearly better symptomatic outcomes from PPI therapy in erosive GERD than nonerosive disease. For erosive GERD, LA classification grades C and D provide the most consistent evidence of GERD[8,118]. LA classification grade B oesophagitis also prompts medical management with acid suppression[8]; however, this grade might not be sufficient evidence for a recommendation of ARS in the absence of alternate phenotypic GERD evidence. LA classification grade A oesophagitis is frequently encountered in asymptomatic healthy volunteers and does not provide conclusive evidence for GERD[119].

Box 3 | **Open research questions**

- Understanding mechanisms of pathological acid reflux in terms of abnormalities of oesophageal and oesophagogastric junction structure and function, including the acid pocket
- Clarification as to whether pathological acid reflux is the cause of abnormal oesophageal motor function, or if reflux is the consequence of abnormal motor function in GERD
- Exploration of the clinical utility of existing and novel oesophageal physiological metrics from high-resolution manometry and ambulatory reflux monitoring in identifying GERD phenotypes that predict GERD management outcome
- Elucidation of the importance of oesophageal sensitivity as a mechanism for GERD symptom reporting and a potential target for treatment

Evidence of reflux on ambulatory reflux monitoring prompts initiation or escalation of acid-suppressive therapy (FIG. 3), and pathological AET is a predictor of good outcome from both medical and ARS therapy[81,92,93]. Within abnormal AET cohorts, those with positive symptom–reflux association (FIG. 4d) have the highest likelihood of improvement from antireflux therapy[78–80]. Thus, the GERD phenotype with the strongest evidence consists of pathological AET associated with positive symptom–reflux association, especially if both SAP and symptom index are positive[80,93]. Antacids and alginates can treat infrequent or breakthrough reflux symptoms[120]. Baclofen, a γ-aminobutyric acid type B receptor agonist, can reduce reflux events by inhibiting TLESRs, with potential adjunctive symptomatic benefit when this drug is available[121]. ARS might be a consideration that can be explored in some patients, especially when EGJ disruption is documented. By contrast, physiological AET with no symptom–reflux association predicts suboptimal outcomes from antireflux therapy and can overlap with functional oesophageal syndromes. Coexisting functional syndromes (functional dyspepsia, IBS) might also predict suboptimal outcome from antireflux therapy[122,123] and might prompt treatment with neuromodulators[38].

Reflux hypersensitivity (physiological acid burden with positive symptom–reflux association) represents a challenge in interpretation and management. The prevalence of reflux hypersensitivity is higher when pH impedance is employed for reflux monitoring compared with pH monitoring alone[124]. When symptom–reflux association is recorded with impedance-detected reflux events, antireflux management approaches (including ARS) might be successful, especially if evidence for EGJ disruption and/or hiatus hernia exists[125,126]. Although true acid sensitivity (symptom associated with pH-detected reflux events alone) is relatively rare, this occurrence is associated with suboptimal response to antireflux therapy[125] and treatments similar to those for functional oesophageal syndromes (for example, neuromodulators) might provide a better outcome than with antireflux therapy alone[38].

Conditions mimicking GERD

Of patients referred with refractory reflux symptoms, at least 30% have functional heartburn, rumination syndrome or achalasia rather than GERD[127] (TABLE 1). In the achalasia spectrum disorders, retrosternal discomfort and regurgitation occur as a consequence of oesophageal outflow obstruction rather than from reflux[127,128]. Within patients referred for ARS, ~1% are diagnosed with achalasia by oesophageal HRM, and an additional 1.5% have evidence of EGJ outflow obstruction[26]. The diagnosis of achalasia and EGJ outflow obstruction have profound clinical importance, as invasive management for these conditions (EGJ disruption) is contradictory to that performed in GERD (EGJ enhancement with ARS).

Rumination syndrome consists of voluntary contraction of abdominal wall musculature during periods of crural diaphragm relaxation, leading to a sharp increase in intra-abdominal pressure that forces gastric content through the oesophagus into the mouth[129]. This increase in intra-abdominal pressure can be identified in the form of an 'r' wave on prolonged HRM with impedance in the post-prandial period. Ambulatory pH-impedance monitoring, however, does not discriminate a rumination episode from a reflux episode[130,131].

Supragastric belching starts with air forced into the oesophagus by contraction of the diaphragm, creating negative pressure in the oesophagus, followed by contraction of abdominal and thoracic muscles resulting in immediate expulsion in the form of a belch[131]. Less commonly, air is swallowed into the stomach and expelled out by a mechanism similar to rumination. In addition to careful history and clinical observation, supragastric belching can be identified on concurrent HRM with impedance.

Oesophageal symptoms can be associated with conditions such as eosinophilic oesophagitis, lichen planus and infectious oesophagitis (oesophageal candidiasis, herpes simplex oesophagitis, cytomegalovirus oesophagitis). Finally, functional disease can give rise to any oesophageal symptom, including symptoms similar to GERD[38]. Ambulatory reflux monitoring demonstrates physiological reflux parameters, but minor motor disorders and contraction-wave abnormalities on HRM are compatible with functional oesophageal disorders[38].

Conclusions

Combining existing data on reflux testing with expert consensus opinion, this Consensus Statement describes the modern evaluation of GERD, especially when oesophageal symptoms persist despite empiric antisecretory therapy and when EGD does not identify an alternate mechanism for symptoms. In this setting, HRM identifies motor pathophysiology conducive to gastroesophageal reflux and ambulatory reflux monitoring describes pathological oesophageal reflux burden and symptom–reflux association. Other novel parameters on pH testing or pH-impedance testing, including MNBI and the PSPW index, might complement conventional reflux parameters in improving confidence for a reflux diagnosis. In the future, understanding GERD pathophysiology in more detail, particularly the inter-relationship between GERD and oesophageal motor dysfunction, and evaluating oesophageal reflux burden with novel metrics could help identify GERD phenotypes better and improve management outcomes (BOX 3). A need now exists for prospective and collaborative outcome studies to determine the clinical value of oesophageal function testing in predicting symptomatic outcome.

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FURTHER INFORMATION

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