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Updates to the modern diagnosis of GERD: Lyon consensus 2.0

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ABSTRACT

The Lyon Consensus provides conclusive criteria for and against the diagnosis of gastro-oesophageal reflux disease (GERD), and adjunctive metrics that consolidate or refute GERD diagnosis when primary criteria are borderline or inconclusive. An international core and working group was assembled to evaluate research since publication of the original Lyon Consensus, and to vote on statements collaboratively developed to update criteria. The Lyon Consensus 2.0 provides a modern definition of actionable GERD, where evidence from oesophageal testing supports revising, escalating or personalising GERD management for the symptomatic patient. Symptoms that have a high versus low likelihood of relationship to reflux episodes are described. Unproven versus proven GERD define diagnostic strategies and testing options. Patients with no prior GERD evidence (unproven GERD) are studied using prolonged wireless pH monitoring or catheter-based pH or pH-monitoring off antisecretory medication, while patients with conclusive GERD evidence (proven GERD) and persisting symptoms are evaluated using pH-impedance monitoring while on optimised antisecretory therapy. The major changes from the original Lyon Consensus criteria include establishment of Los Angeles grade B oesophagitis as conclusive GERD evidence, description of metrics and thresholds to be used with prolonged wireless pH monitoring, and inclusion of parameters useful in diagnosis of refractory GERD when testing is performed on antisecretory therapy in proven GERD. Criteria that have not performed well in the diagnosis of actionable GERD have been retired. Personalisation of investigation and management to each patient's unique presentation will optimise GERD diagnosis and management.

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The Lyon Consensus proposes conclusive criteria for and against the diagnosis of gastro-oesophageal reflux disease (GERD), and adjunctive metrics that either consolidate or refute GERD diagnosis when primary criteria are inconclusive.[1] New published research indicates that testing strategies and thresholds differ when investigating patients with unproven versus proven GERD. The definition of GERD needed to be updated following improved specificity of diagnostic testing. Finally, as ROME V diagnostic criteria are being developed for oesophageal disorders of gut–brain interaction (DGBI), specific criteria for diagnosis and exclusion of GERD were needed that were consistent with emerging research. For several reasons (table 1), an update of the original Lyon Consensus is essential and timely.

The current update of the Lyon Consensus seeks to improve specificity of the modern diagnosis of GERD, to make oesophageal diagnostic algorithms congruent for identification of conclusive GERD, and for exclusion of GERD when favouring DGBI or other oesophageal disorders. Additionally, Lyon Consensus 2.0 defines GERD considering recent evidence, describes 'actionable' GERD where evidence from oesophageal testing supports revising, escalating or personalising GERD management, and identifies symptoms that have a high versus low likelihood of pathophysiological relationship to reflux episodes.

METHODS

The Lyon Consensus steering committee developed a strategy for this update in October 2022, and a core group reviewed recent literature. Five topics were identified as key areas in need of update (table 1), and statements were developed to address these (table 2). An international working group was assembled in January 2023, selected based on expertise in GERD diagnosis and management, ongoing research, geographical and gender representation as well as availability for virtual and in-person meetings. The core and working groups totalled 21 members, consisting of 20 voting members, and one non-voting member (MRF) who reviewed created content. The statements were further refined during virtual meetings in February–April 2023. The Lyon 2.0 core and working groups anonymously recorded levels of agreement for each statement using an electronic survey generated using REDCap and hosted at the University of California, San Diego.

The RAND/University of California Los Angeles Appropriateness Methodology was used to assess levels of agreement. As per this methodology, members were instructed to apply their ranking to the average patient presenting to the average

Table 1 Justification of update of the Lyon Consensus

Key areas in need for update identified by the steering committee	Entities not covered in original Lyon Consensus	Entities covered in update of Lyon Consensus
Modern definition of actionable GERD in the context of presenting symptoms	Concept of 'actionable GERD'	Description of conclusive GERD where oesophageal testing supports revising, escalating or personalising GERD management
	Modern definition of GERD	Definition of GERD that takes both troublesome symptoms and oesophageal test results into consideration; criteria that rule out GERD are also defined, for use in diagnostic criteria for disorders of gut–brain interaction
	Differential approach to oesophageal evaluation based on presenting symptoms and prior GERD evidence	Description of oesophageal symptoms that have high, intermediate and low likelihood of association with reflux episodes; concept of proven versus unproven GERD in determining testing strategy
Objective endoscopic findings of GERD	LA grade B was considered inconclusive evidence for GERD	LA grade B oesophagitis is considered conclusive evidence of GERD, based on recent studies using prolonged pH monitoring and pH-impedance monitoring that corroborate earlier data from pH-monitoring
	Discussion of endoscopic findings off versus on antisecretory therapy	Need for performing endoscopy off antisecretory therapy in unproven GERD; endoscopic findings that confirm GERD when tested on optimised therapy
	The specific value (or lack thereof) of supportive endoscopic findings	Hiatus hernia on endoscopy is considered supportive evidence for GERD; routine standard biopsy evaluation is not recommended or helpful; endoscopy-based mucosal impedance evaluation needs further research
Wireless pH monitoring indications and metrics	Wireless pH monitoring was not discussed	Indications, thresholds, value and utilisation of wireless pH monitoring is discussed in detail
pH-impedance monitoring indications and metrics off antisecretory therapy	Specific indications for pH-impedance monitoring were not discussed	Presentations where pH-impedance monitoring has advantage over pH-only or wireless pH monitoring are specifically discussed
	Thresholds for mean nocturnal baseline impedance were not elaborated	Thresholds for mean nocturnal baseline impedance are provided and discussed; postreflux swallow induced peristaltic wave index is retired as adjunctive evidence
pH impedance monitoring indications and metrics on anti-secretory therapy in diagnosis of refractory GERD	pH-impedance monitoring was not discussed in the context of on-therapy testing	Indications, metrics and thresholds are provided for use of pH-impedance monitoring on therapy in proven GERD

GERD, gastro-oesophageal reflux disease; LA, Los Angeles .

physician at an average facility, without considering cost implications, insurance reimbursement or feasibility at their individual centre. Each statement was ranked on a 9-point scale, where median scores of 1–3 were considered inappropriate, 4–6 were of uncertain appropriateness and 7–9 were considered appropriate and meeting agreement. Panel members provided input and statements of uncertain appropriateness were revised or consolidated after the first and second rounds of voting in March–April 2023. All revised and consolidated statements met appropriateness after the third round of voting, meeting the a priori threshold of 80% agreement (table 2). The final meeting was held in May 2023.

STATEMENTS

GERD definition

The modern definition of actionable GERD requires conclusive evidence of reflux-related pathology on endoscopy and/or abnormal reflux monitoring (using Lyon consensus thresholds) in the presence of compatible troublesome symptoms.

Troublesome typical symptoms alone may be enough for antisecretory medication trials, but up-front oesophageal testing is suggested for all other symptom categories and in proton pump inhibitor (PPI) non-responders, prior to invasive GERD management or prior to long-term medical management.

Actionable GERD constitutes settings where management requires long-term acid suppression, an escalation of medical management, or consideration of interventional (ie, not easily reversible) management options for GERD such as laparoscopic fundoplication, magnetic sphincter augmentation (MSA), endoscopic GERD therapies or bariatric surgery, where high confidence in GERD diagnosis is essential.

The Montreal consensus defines GERD as the reflux of stomach contents into the oesophagus causing troublesome symptoms and/or complications.[2] However, not all 'troublesome' symptoms can be directly linked to reflux of gastric content, and symptoms alone are insufficient for a conclusive diagnosis. Nevertheless, pragmatic continuation of empiric antisecretory therapy is considered appropriate when typical symptoms (heartburn, chest pain, regurgitation) improve with GERD treatment trials[3] (figure 1), although response could also be due to placebo effect.[4 5] In parallel, assumptions of GERD relationships with cough, hoarseness and other 'isolated' extraoesophageal symptoms (ie, in the absence of typical GERD symptoms) overestimated atypical GERD diagnoses leading to inappropriate use of antisecretory drugs, high economic burden and waste of limited testing resources[6 7] (figure 1). Use of Lyon consensus criteria is anticipated to improve diagnostic specificity and confidence. While objective testing prior to long-term medical management of typical symptoms is optimal, practicality and cost-effectiveness need further study.

Table 2 Statements and levels of agreement among the core and working groups

Statements	Median score	% agreement
The modern definition of actionable GERD requires evidence of conclusive reflux-related pathology on endoscopy, and/or abnormal reflux monitoring (using Lyon Consensus thresholds) in the presence of compatible troublesome symptoms.	8.5	94
Troublesome typical symptoms alone may be enough for antisecretory medication trials, but up-front oesophageal testing is suggested for all other symptom categories and in PPI non-responders, prior to invasive GERD management or prior to long-term medical management.	9	89
Typical symptoms of GERD consist of heartburn, oesophageal chest pain and regurgitation.	9	100
The relationship of belching to reflux disease is variable, but belching can be part of reflux pathophysiology.	8.5	89
Chronic cough and wheezing have a low but potential pathophysiological relationship to reflux disease.	8	83
Hoarseness, globus, nausea, abdominal pain and other dyspeptic symptoms in the absence of typical symptoms have a low likelihood of pathophysiological relationship to reflux disease.	8	95
LA grades B, C and D oesophagitis, biopsy proven Barrett's oesophagus and peptic stricture are conclusive for a diagnosis of GERD.	9	94
To maximise the diagnostic yield, endoscopy should be performed 2–4 weeks after discontinuation of PPI therapy in unproven GERD.	8	83
LA grades B, C and D oesophagitis and recurrent peptic stricture while on optimised PPI therapy are indicative of refractory GERD.	9	89
Prolonged wireless pH monitoring off antisecretory therapy is the preferred diagnostic tool in unproven GERD when available, and may provide highest diagnostic yield with study duration of 96 hours.	8	90
Ambulatory pH-impedance monitoring off antisecretory therapy has diagnostic value in unproven GERD when typical reflux symptoms are associated with excessive belching, when rumination is suspected, and when pulmonary symptoms are being evaluated for association with GERD.	8	85
Ambulatory pH-impedance monitoring on PPI is of value in proven GERD with persisting symptoms despite optimal therapy.	9	94
AET<4.0% on all days of wireless pH monitoring with negative reflux-symptom association excludes GERD.	8.5	100
AET>6.0% for ≥2 days is diagnostic of GERD and supports treatment for GERD.	9	89
AET<4.0% on all days with positive reflux-symptom association meets criteria for reflux hypersensitivity.	8	94
Any prolonged wireless pH monitoring study that does not meet criteria for GERD, reflux hypersensitivity or a normal study is considered inconclusive for GERD.	8	83
Total AET >6% off PPI on ambulatory pH monitoring is diagnostic of GERD and supports treatment for GERD.	9	94
Total reflux episodes <40/day is adjunctive evidence for absence of pathological GERD.	8	94
Total reflux episodes 40–80/day off PPI is inconclusive evidence for GERD as a stand alone metric.	8	100
Total reflux episodes >80/day is adjunctive evidence for objective GERD.	8	100
There are not sufficient data regarding thresholds for upright versus supine reflux episode numbers, and acidic versus non-acidic reflux events to incorporate these findings into clinical practice.	8	94
Combination of AET>4% and >80 reflux episodes on an optimised antisecretory regimen is evidence for actionable refractory GERD.	8	95
Baseline impedance of <1500 ohms is adjunctive evidence for GERD, while baseline impedance >2500 ohms is evidence against pathological GERD.	8	90

AET, acid exposure time; GERD, gastro-oesophageal reflux disease; LA, Los Angeles; PPI, proton pump inhibitor.

GERD symptoms

Typical symptoms of GERD consist of heartburn, oesophageal chest pain and regurgitation.

The relationship of belching to reflux disease is variable, but belching can be part of reflux pathophysiology.

Chronic cough and wheezing have a low but potential pathophysiological relationship to reflux disease.

Hoarseness, globus, nausea, abdominal pain and other dyspeptic symptoms in the absence of typical symptoms have a low likelihood of pathophysiological relationship to reflux disease.

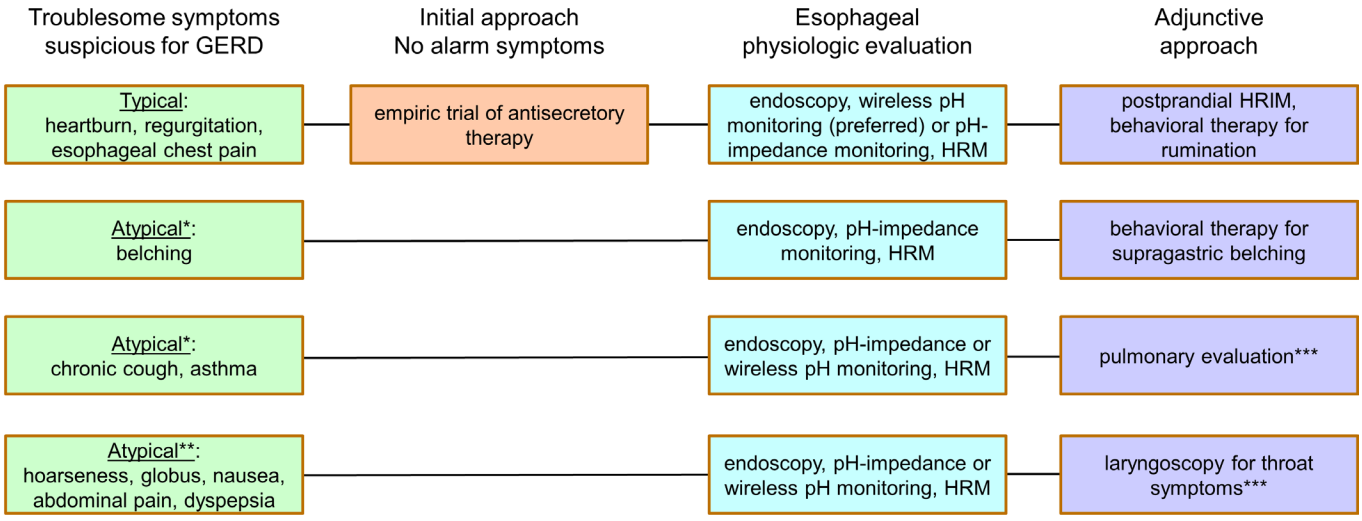
The modern diagnosis of GERD starts with identification of troublesome symptoms, but not all symptoms carry equal weight. Burning sensations beneath the breast bone (heartburn) or retrosternal chest pain may be interchangeable when responsive to empiric anti-secretory medication,[8] especially after a cardiac aetiology for chest pain is ruled out.[9] Approximately two-thirds to three-quarters of patients with heartburn, and half of patients with non-cardiac chest pain report response to short-term antisecretory therapy, but a 10%–25% placebo effect can confound this response; thus, response to an empiric PPI trial alone is insufficient for a conclusive GERD diagnosis.[10] Both heartburn and chest pain can arise from motor disorders (such as achalasia) and DGBI mechanisms.[9 11]

Regurgitation, the effortless presence of sour or bitter gastric content in the mouth, often does not fully improve with acid suppression alone.[12] Acidic reflux episodes become weakly acidic or non-acidic following antisecretory therapy,[13] regurgitation of which can be an important mechanism for refractory GERD leading to clinically relevant, incremental decline in health-related quality of life.[14 15] Regurgitation needs differentiation from rumination, a subconsciously learnt postprandial behaviour, sometimes pleasurable, that typically stops when the regurgitate becomes acidic[16]; this can be mistaken for PPI-refractory GERD.[17] Rumination is treated with behavioural therapy rather than acid suppression or antireflux surgery (ARS) (figure 1).[18]

Both supragastric belching (where air ingested or injected into the oesophagus does not reach the stomach before eructation) and gastric belching (where air in the proximal stomach is vented during a transient LES relaxation) can trigger reflux.[19] Belching (and lack thereof, abelchia) can also be part of behavioural syndromes without pathological reflux (figure 1).

Chronic cough and wheezing have a significantly lower likelihood of direct reflux aetiology compared with typical symptoms (figure 1). Chronic cough may represent hyper-responsive behaviour, where reflux is one of several triggers for coughing bouts, such as abrupt changes in temperature or humidity, prolonged talking or voice use, strong odours or scents, food triggers and postnasal drip.[20] Refluxate aspirated into the airways has been implicated in graft failure after lung transplant, and in the pathogenesis of idiopathic pulmonary fibrosis.[21 22] Wheezing and asthma may rarely be triggered by reflux, when aggressive reflux management may provide better control of asthma.[23]

Data demonstrating response of globus to GERD management are scarce.[24] Hoarseness, throat clearing and sore throat have even less robust reflux associations,[8 25] and these symptoms often correlate with cognitive processes with or without reflux disease.[26] While dysphagia can be



* likelihood of GERD is lower than with typical symptoms, testing is performed to identify or rule out a reflux basis for symptoms
** likelihood of GERD is very low, upfront testing is typically not recommended except to rule out a reflux basis for symptoms
***adjunctive approaches may precede esophageal evaluation to rule out primary pulmonary and laryngeal disorders

Figure 1 Troublesome typical and atypical symptoms suspicious for gastro-oesophageal reflux disease (GERD), and usual approach to evaluation of these symptoms. An empiric trial of antisecretory therapy is appropriate for typical symptoms in the absence of alarm symptoms. Prolonged wireless pH monitoring is most appropriate for quantification of reflux burden with typical symptoms, although pH-impedance or even pH only monitoring may be options depending on availability and expertise. Belching, cough and asthma may have a potential association with reflux episodes. Supragastric belching and rumination need to be identified, preferably using high-resolution impedance manometry (HRIM) and managed with behavioural therapy. Up-front testing is performed primarily to rule out a reflux basis for symptoms for all other atypical symptoms. Pulmonary evaluation and laryngoscopy serve to rule out primary non-GERD disorders, and may precede oesophageal physiological testing.

a consequence of reflux-induced oesophageal strictures or advanced erosive oesophagitis, primary dysphagia without heartburn, especially with bolus impaction, may suggest eosinophilic oesophagitis or a motility disorder. Finally, epigastric and abdominal symptoms (nausea, abdominal pain) are unlikely to have a reflux aetiology (figure 1) where reflux monitoring is typically not recommended, the exception being mischaracterisation of heartburn as epigastric burning.[27]

GERD evidence

Endoscopy

LA grades B, C and D oesophagitis, biopsy proven Barrett's oesophagus and peptic stricture are conclusive for a diagnosis of GERD.

Evidence of visible oesophageal mucosal damage typical of reflux induced injury and GERD-related complications (oesophageal stricture, Barrett's oesophagus) are consistently associated with high reflux burden, and symptom improvement with GERD management.[28–31] The Los Angeles (LA) classification of erosive oesophagitis was established to provide a unifying global classification for oesophagitis.[30 32] Initial validation indicated that LA grade A oesophagitis had a kappa value of 0.65 and higher acid exposure time (AET) than non-erosive reflux disease (NERD) (9.3% vs 6.7%, respectively),[32] later studies have demonstrated grade A oesophagitis in 5%–7.5% of healthy subjects.[29 30 33 34] In contrast, LA grades B, C and D oesophagitis are highly uncommon in healthy subjects.[29] LA grade B oesophagitis demonstrated AET similar to grade C in the original validation study (13.7% vs 11.7%, respectively),[32] as well as in recent reports using wireless pH monitoring (8.23% vs 9.95%, respectively)[29] and pH-impedance monitoring (6.0% vs 8.7%, respectively).[28] Furthermore, symptom response with PPI is similar between LA grades B and C oesophagitis (74% vs 70%, respectively).[28] Grade D is associated with the highest mean AET among LA grades (19.1%).[32]

These findings indicate that, contrary to the original Lyon Consensus, well-characterised LA grade B oesophagitis represents conclusive evidence for GERD and does not require further confirmation with reflux monitoring prior to management. However, objective GERD can overlap with DGBI phenotypes in symptomatic patients, which needs consideration when planning invasive GERD management options.[35]

To maximise the diagnostic yield, endoscopy should be performed 2–4 weeks after discontinuation of antisecretory therapy in unproven GERD.

Since mucosal healing occurs with PPIs in approximately 80%,[36] the likelihood of finding significant oesophagitis is greatly reduced if endoscopy is performed after 8 weeks of PPI therapy. To make a conclusive diagnosis in previously unproven GERD and to adequately phenotype patients to NERD versus erosive oesophagitis, endoscopy is optimally performed after withholding PPI therapy. If endoscopy is performed too soon, a lower grade of oesophagitis or no oesophagitis may be observed, which may not accurately represent the GERD phenotype. While several studies report endoscopic relapse of oesophagitis in approximately 70% at 6 months after PPI withdrawal,[37] the timing of relapse is unknown, and is probably related to pretreatment oesophagitis severity. In a small prospective study of 12 patients with

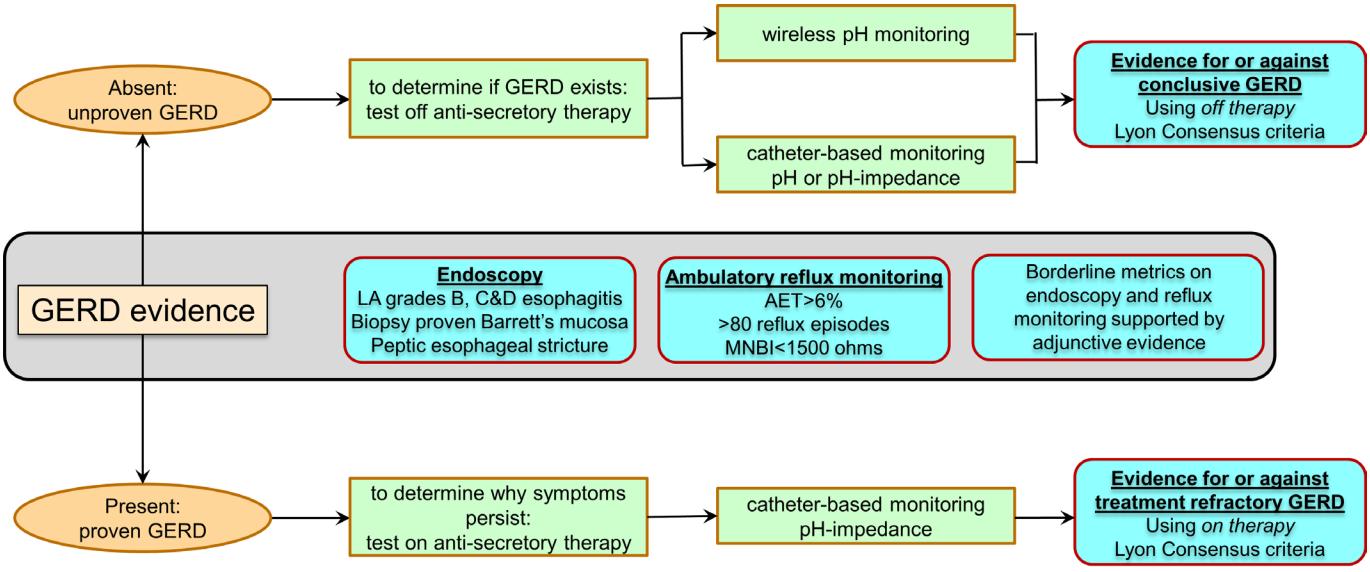


Figure 2 The presence or absence of prior conclusive evidence for gastro-oesophageal reflux disease determines test strategy and methodology. When conclusive GERD evidence is absent (unproven GERD), testing is performed to establish or refute the presence of GERD, hence ambulatory reflux monitoring is performed off antisecretory therapy. Wireless pH monitoring and catheter based pH or pH monitoring are alternatives, based on local feasibility, availability and cost of each technique. Conclusive GERD evidence, and borderline evidence with supportive adjunctive metrics according to the Lyon Consensus (figure 3) serve to provide evidence of GERD. In contrast, when symptoms persist despite adequate therapy of previously proven GERD, pH-impedance monitoring is performed on therapy to look for evidence for treatment refractory GERD necessitating management escalation. AET, acid exposure time; GERD, gastro-oesophageal reflux disease; LA, Los Angeles; MNBI, mean nocturnal baseline impedance.

healed LA grade C oesophagitis, discontinuation of therapy led to oesophagitis recurrence after just 1 week in 10 patients, with 5 patients demonstrating recurrent grade C oesophagitis after 2 weeks.[38] However, these results may not necessarily be extrapolated to lower grade oesophagitis. Therefore, for accurate GERD phenotyping, endoscopy should be performed after a minimum of 2 weeks but preferably 4 weeks after PPIs discontinuation.

LA grade B, C and D oesophagitis and recurrent peptic stricture on endoscopy while on optimised antisecretory therapy are indicative of refractory GERD.

The persistence of inflammatory and/or fibrotic mucosal lesions despite optimised PPI therapy is indicative of refractory GERD. Since most patients with refractory symptoms and proven GERD have a normal endoscopy, the presence of mucosal breaks consistent with LA grade B or greater despite 8 weeks of PPI therapy may reflect poorly controlled acid reflux despite downstaging of initial oesophagitis grade.[39] Regardless whether patients are symptomatic or not, this should be considered diagnostic of ongoing or treatment-refractory GERD.[39]

Ambulatory reflux monitoring

Choice of ambulatory reflux monitoring methodology

Prolonged wireless pH-monitoring off antisecretory therapy is the preferred diagnostic tool in unproven GERD when available and may provide highest diagnostic yield with study duration of 96 hours.

As many as 70% of symptomatic patients have endoscopically normal oesophageal mucosa. During this index endoscopy, a wireless pH probe can be placed to monitor AET for up to 96 hours, which takes day-to-day AET variation into account, with better patient tolerance while also shortening diagnostic delay.[40–45] The prognostic performance of wireless reflux monitoring was significantly higher with 72–96 hours monitoring compared with data from the first 48 hours (area under curve (AUC) 0.63 for 96-hour data vs 0.57 for 48-hour data, p=0.01), which implies an inherent benefit over 24-hour pH monitoring despite lack of high-quality head-to head-comparisons.[46] The third and fourth days of wireless pH monitoring add significantly to determining a dominant physiological versus pathological AET pattern, and allow discontinuation of PPI when a dominant physiological pattern is identified.[42 45 46] Thus, 96-hour pH monitoring predicts discontinuation of PPI versus ongoing need for PPI therapy better than shorter durations of monitoring (figure 2). However, wireless pH monitoring is not available, feasible or affordable worldwide. Ambulatory catheter-based reflux monitoring remains a viable alternative, and each clinician needs to personalise the optimal testing option for individual patients, taking resources, cost and patient presentation into consideration.

Ambulatory pH-impedance monitoring off antisecretory therapy has diagnostic value in unproven GERD when typical reflux symptoms are associated with excessive belching, when rumination is suspected, and when pulmonary symptoms are being evaluated for association with GERD.

While pH-impedance monitoring performed off PPI provides similar 24-hour AET data as catheter-based pH monitoring or day 1 of wireless pH monitoring, more reflux episodes are detected because of higher sensitivity of the impedance component in identifying reflux episodes independent of pH.[47] Accurate reflux episode counts predict GERD symptom response when elevated, especially in regurgitation-predominant GERD,[48] although expert interpretation is required to overcome inaccuracies of automated analysis.[49] Additionally, the use of pH-impedance monitoring over pH monitoring alone shifts diagnoses from functional heartburn to reflux hypersensitivity, since additional reflux episodes identified irrespective of acidic content using pH-impedance monitoring may be associated with

symptoms.[50 51] Mean nocturnal baseline impedance (MNBI) measurement from pH-impedance monitoring provides longitudinal evidence of reflux-induced mucosal damage,[52–54] but post-reflux swallow induced peristaltic wave (PSPW) analysis remains predominantly a research tool useful in phenotyping rather than diagnosing GERD.[52 55–57]

High AET is uncommon in patients with 'isolated' extraoesophageal symptoms, and pH-impedance monitoring seems to improve diagnostic yield,[58] partly because of the added value of reflux number counts, reflux-symptom association testing, and parameters like MNBI. A study of 156 patients with chronic cough undergoing pH-impedance found that pathological AET and low baseline impedance increased the probability of PPI response.[59] In small prospective cohorts of patients with laryngeal symptoms and laryngoscopic signs suspicious for reflux, pH-impedance testing off PPI therapy confirmed GERD in less than a fifth of patients independent of symptoms or laryngoscopic findings, suggesting that pH-impedance monitoring up front has important value in identifying the select few patients with extraoesophageal symptoms who could benefit from anti-reflux therapy[58 60] (figure 1). Up-front physiological testing is more cost-effective than empiric PPI therapy with extra-oesophageal symptoms, given the high numbers needed to treat for PPI response.[8 61]

Ambulatory pH-impedance monitoring is the gold standard for diagnosing supragastric belching, identified as rapid anterograde increase in intraoesophageal impedance, followed by prompt retrograde decline to baseline values.[19] Using pH-impedance monitoring, supragastric belching episodes were identified in 48% of 50 consecutive GERD patients (median 13 episodes/24 hours) compared with median 2 episodes in 50% of 10 healthy volunteers.[62] In contrast, rumination episodes are not distinguishable from reflux episodes on pH-impedance monitoring, but typically extend to the proximal oesophagus, with prompt symptom reporting and higher prevalence in the immediate postprandial period,.[17 63]

Thus, pH-impedance monitoring off antisecretory therapy has the same indications as wireless pH monitoring, and has particular value when evaluating belching, predominant regurgitation, and supraoesophageal or pulmonary symptoms (figure 2). Catheter-based pH monitoring will suffice when pH-impedance monitoring is not available, but this technique cannot detect supragastric belching or rumination, and has lower sensitivity for accurate reflux episode counts which compromises reflux-symptom association.

Ambulatory pH-impedance monitoring on PPI is of value in proven GERD with persisting symptoms despite optimal therapy.

When pH-only testing is performed on PPI, very low AET values are recorded: median AET was 1.2% on once-daily PPI and 0.3% on a twice-daily regimen in 131 patients with both typical and atypical reflux symptoms.[64] Similarly low values were reported in 66 healthy volunteers undergoing pH-impedance testing on twice-daily PPI.[65] Although acidic reflux episodes generally become weakly acidic or non-acidic on PPI, both can be detected using pH-impedance monitoring, and symptoms could be triggered by persisting reflux episodes independent of pH.[13] In a study of 39 patients with refractory reflux symptoms tested both on therapy (pH-impedance monitoring) and off therapy (wireless pH monitoring), abnormal AET off therapy was associated with weakly acid reflux episodes on therapy.[66] Further, MNBI from pH-impedance monitoring on therapy may have diagnostic value, while PSPW remains a research tool in further phenotyping patients with previously proven GERD.[56 67 68]

Ambulatory pH-impedance monitoring performed on antisecretory medications may help decision-making regarding escalation of GERD management beyond pharmacotherapy. In a randomised trial comparing ARS to medical management in patients with heartburn incompletely responding to PPI, although the likelihood of abnormal reflux burden on pH-impedance monitoring was small (78 patients from a starting cohort of 366 patients, 21%), ARS resulted in symptom relief in 67% among 27 patients, in contrast to 28% with continued medical management ($p<0.001$).[69] In another study of 85 patients with heartburn and regurgitation in the context of previously proven GERD studied with pH-impedance testing on twice a day PPI regimen, AET >4.0% and/or >80 reflux episodes resulted in 85% reporting symptom benefit from MSA when this was offered, especially when regurgitation was the dominant symptom (93%) compared with heartburn (60%).[65] Abnormal pH-impedance metrics on once-daily PPI therapy normalised with maximal PPI therapy in 71.1% of 45 symptomatic patients.[70] Further, 89% of 38 patients with refractory reflux symptoms and abnormal pH-impedance metrics on maximal PPI therapy benefited from ARS on retrospective analysis.[70]

Thus, in patients with proven GERD and persisting symptoms, pH-impedance monitoring on therapy can help phenotype patients and identify ongoing reflux burden that may respond to ARS, irrespective of how GERD was previously proven[3 71] (figure 2).

Metrics and thresholds useful in ambulatory reflux monitoring

Wireless pH monitoring

AET<4.0% on all days of wireless pH monitoring with negative reflux-symptom association excludes GERD.

A recent study examining various AET thresholds on wireless pH monitoring identified AET<4.0% with the highest predictive value for PPI discontinuation while maintaining a minimal symptom burden.[42] Studies using wireless pH monitoring in healthy controls have also demonstrated predominance of median AET<4.0%, thus supporting the Lyon Consensus designation of AET<4.0% as physiological acid exposure.[29 45] Further, the number of days with AET<4.0% was of prognostic value, where the odds of PPI discontinuation was 10 times greater with AET<4.0% across all 4 days of monitoring.[42] Therefore, in patients with unproven GERD who report heartburn, regurgitation and/or oesophageal chest pain, AET<4.0% across all days of prolonged wireless pH monitoring off PPI therapy excludes pathological GERD.

AET>6.0% for ≥2 days is diagnostic of GERD and supports treatment for GERD.

AET>6.0% denotes pathological oesophageal acid burden.[1] Patients meeting the threshold of ≥2 days with AET>6% are more likely to have symptoms, especially typical GERD symptoms, higher GERDQ scores, erosive oesophagitis and higher likelihood of needing PPI therapy.[29 42 45] Therefore, AET>6% on at least 2 days of wireless pH monitoring is diagnostic of GERD requiring treatment.[41 45]

AET<4.0% on all days with a positive reflux-symptom association meets criteria for reflux hypersensitivity.

Positive symptom association probability (>95%) and/or symptom index >50% increase confidence that symptoms may

be linked to reflux episodes.[1] Rome IV posits that positive reflux-symptom association with physiological AET establishes reflux hypersensitivity as a mechanism for symptoms, where neuromodulators may complement antisecretory therapy.[72] However, reflux-symptom association may not always be reliable, since it relies on prompt patient reporting of perceived symptoms within a 2 min window.[73]

Any prolonged reflux monitoring study that does not meet criteria for GERD, reflux hypersensitivity or a normal study is considered inconclusive for GERD.

When AET is between 4.0% and 6.0%, further clinical context and additional test data are needed to determine the need for GERD management,[1] since other conditions including reflux hypersensitivity, motility disorders and behavioural disorders such as supragastric belching and rumination may be contributing to patient symptoms. This is supported by data from studies on healthy volunteers where 20% had dominant borderline AET values across 4 days of recording despite being asymptomatic,[45] and patients with normal endoscopy and low-grade oesophagitis (LA Grade A) had AET values overlapping this borderline range.[29]

pH-impedance monitoring

Total AET>6% off PPI on ambulatory pH-impedance monitoring is diagnostic of GERD and supports treatment for GERD.

Among the various oesophageal pH monitoring parameters acquired from catheter-based studies, total AET>6% off antisecretory medications has long been considered the most reproducible and specific metric for identifying GERD that will respond to medical or surgical treatment.[1 74] Thresholds for pH-impedance metrics have been based on small single-region studies using inconsistent criteria for confirming reflux events. Noting these limitations, one recent study performed expert consensus analysis of 391 impedance-pH tracings from countries around the world using either the Diversatek or Laborie systems.[75] The investigators identified normative thresholds for AET that substantiate the Lyon Consensus threshold (<4%), with significant differences between Diversatek (95th percentile 2.8%) and Laborie (95th percentile 5%) systems, and significant differences across countries and regions. Thus, clinical interpretation of pH-impedance monitoring studies should take into account these substantial system-related and region-related differences in normal impedance-pH monitoring thresholds.

Total reflux episodes <40/day is adjunctive evidence for absence of pathological GERD.

Total reflux episodes 40–80/day off PPI is inconclusive evidence for GERD as a stand-alone metric.

Total reflux episodes >80/day is adjunctive evidence for objective GERD.

There are not sufficient data regarding thresholds for upright versus supine reflux episode numbers, and acidic versus non-acidic reflux events to incorporate these findings into clinical practice.

In addressing the clinical relevance of numbers of reflux episodes, a study of off-therapy pH-impedance tracings from 488 patients with PPI-dependent heartburn and 70 healthy controls showed that a threshold value of 40 reflux episodes significantly differentiated patients from controls.[53] An expert consensus analysis of 391 pH-impedance studies performed in healthy volunteers demonstrated system differences between Diversatek (95th percentile 55 episodes) and Laborie (95th percentile 78 episodes), with considerable regional variability.[75] A post hoc analysis of 123 patients with troublesome regurgitation on once-daily PPI randomised to twice-daily PPI or MSA found that reduction of total reflux episodes to physiological levels (especially to <35) was associated with improved treatment outcomes, while a preoperative finding of >80 reflux episodes despite twice-daily PPI predicted satisfaction with the outcome of MSA.[48]

In a study of 67 patients with weakly acidic reflux (defined on 24-hour pH-impedance monitoring performed off PPIs as AET<4.2% and total reflux episodes>40), MSA resulted in significant improvements in GERD-related symptoms and quality of life.[76] Another study evaluated 72 patients with GERD symptoms who had 24-hour pH-impedance monitoring performed off PPIs.[77] Using abnormal AET as the gold-standard for GERD diagnosis, AUC analysis showed that a threshold of ≥41 total reflux episodes was optimally sensitive and specific for identifying GERD (sensitivity 69.6%, specificity 80.7%, AUC 0.83, 95% cCI 0.73 to 0.92), although this does not identify reflux episodes as an independent predictor of GERD.[77]

These data support maintaining the reflux episode thresholds for physiological reflux (<40 reflux episodes) and pathological reflux (>80 reflux episodes) defined by the Lyon consensus, with 40–80 reflux episodes deemed inconclusive for GERD as a stand-alone metric.

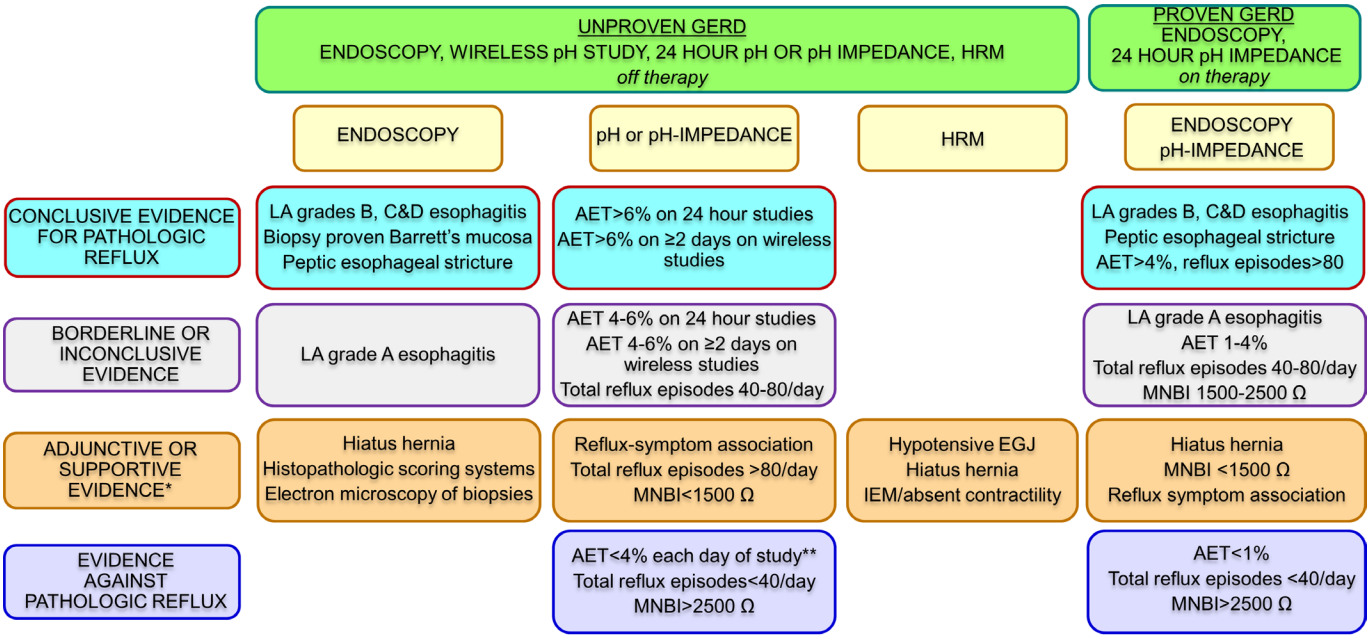
Combination of AET>4% and >80 reflux episodes/day on an optimised antisecretory regimen is evidence for actionable refractory GERD.

A retrospective study evaluated pH-impedance tracings performed on PPIs in 66 healthy volunteers, 43 patients with proven heartburn-predominant GERD, and 42 with proven regurgitation-predominant GERD.[65] When the two GERD groups were pooled for ROC analysis, an AET threshold of 0.5% predicted PPI-non-response with sensitivity of only 0.62, specificity 0.51, AUC 0.58, p=0.22. However, a reflux episode threshold count of 40 performed considerably better with sensitivity 0.80, specificity 0.51, AUC 0.70, p=0.002. The combination of AET>4% and >80 reflux episodes had sensitivity and specificity of 0.50 and 0.71 for predicting PPI non-response; 85% of patients with these parameters who underwent escalation of GERD management to ARS or MSA improved symptomatically. In another study that evaluated 366 patients with persistent heartburn despite bid PPI therapy, an AET threshold of 4.2% (and/or positive symptom association probability) was used to define refractory GERD; using this definition, 67% of 27 patients randomised to ARS improved.[69] These findings suggest that AET of 4.0% and 80 reflux episodes define a need for escalation of reflux management.

Baseline impedance

Baseline impedance of <1500 ohms is adjunctive evidence for GERD, while baseline impedance >2500 ohms is evidence against pathological GERD.

Oesophageal baseline impedance is a marker of oesophageal mucosal integrity, and may add value towards GERD diagnosis, especially when AET is inconclusive.[54] The original description measures MNBI averaged from three different 10 min periods during the supine period that excludes the effect of swallows and reflux episodes.[78] Another method



* factors that increase confidence for presence of pathologic reflux when evidence is otherwise borderline or inconclusive
** wireless pH monitoring: <4% on all days; pH-impedance: all criteria should be met.

Figure 3 Findings that establish conclusive evidence for gastro-oesophageal reflux disease (GERD) can be acquired from endoscopy and/or ambulatory reflux monitoring off therapy in unproven GERD. When evidence is borderline, adjunctive evidence on endoscopy, pH-impedance monitoring and manometry can sway confidence towards or away from conclusive GERD. Findings on pH-impedance monitoring or wireless pH monitoring can establish absence of GERD, especially when endoscopy is also normal. Similar levels of conclusive, borderline and adjunctive metrics are described for endoscopy and pH-impedance monitoring performed on optimised antisecretory therapy. AET, acid exposure time; HRM, high-resolution manometry; IEM: ineffective esophageal motilityl LA, Los Angeles; MNBI, mean nocturnal baseline impedance.

averages impedance values during the entire supine period.[79] Both methods have excellent correlation with each other and can discriminate GERD patients from healthy subjects.

A multicentre international study of healthy asymptomatic subjects undergoing pH-impedance monitoring off PPI demonstrated the fifth percentile MNBI value of 1500 ohms at 3 and 5 cm above the LES, implying impaired oesophageal mucosal integrity below this threshold.[75] Patients with conclusive GERD based on abnormal AET have been demonstrated to have MNBI values consistently below 1500 ohms.[80] Median values in healthy asymptomatic subjects and symptomatic subjects with normal AET were consistently >2500 ohms.[75 80]

UPDATED CRITERIA FOR MODERN DIAGNOSIS OF GERD

The Lyon Consensus 2.0 updates oesophageal test parameters that either conclusively establish or rule out the presence of GERD (figure 3). The existing Lyon Consensus criteria have been updated based on new research, and parameters that have not functioned as diagnostic criteria have been retired (table 3). The concepts of unproven and proven GERD are used

Table 3 Changes from original (Lyon 1.0) to updated (Lyon 2.0) criteria for the modern diagnosis of GERD

	Original Lyon 1.0 criteria	Updated Lyon 2.0 criteria	Retired criteria
Overall		Concepts of different testing strategies in unproven versus proven GERD	
Endoscopy	No criteria for endoscopy performed on therapy	Separate criteria added for testing performed on therapy	
Conclusive endoscopic evidence off therapy	LA C, D oesophagitis	LA B, C, D oesophagitis	
Borderline endoscopic evidence off therapy	LA A, B oesophagitis	LA A ooesophagitis	
Adjunctive endoscopic evidence off therapy	Histopathology (score) Electron microscopy (DIS) Low mucosal impedance	Hiatus hernia Histopathology scoring systems Electron microscopy of biopsies	Routine oesophageal biopsy analysis Endoscopy-based mucosal impedance assessment
pH or pH impedance	No separation between testing off and on antisecretory therapy	Separate thresholds for testing off and on antisecretory therapy	
wireless pH monitoring	No criteria for wireless pH monitoring	Wireless monitoring thresholds added	
pH impedance monitoring	No thresholds for baseline impedance	Thresholds added for mean nocturnal baseline impedance	Postreflux swallow induced peristaltic wave index
High-resolution manometry	Analysis of motor diagnoses using Chicago Classification version 3.0	Analysis of motor diagnoses using Chicago Classification version 4.0	

DIS, dilated intercellular spaces; GERD, gastro-oesophageal reflux disease; LA, Los Angeles.

in recommendations of testing methodology, options, metrics and thresholds. Additionally, Lyon Consensus 2.0 proposes a modern definition of GERD and describes symptoms with high versus low likelihood of objective GERD.

In light of recent reports[28 29] that corroborate evidence from early descriptions of the LA grading of oesophagitis,[30] endoscopic identification of LA grades B, C and D establish the diagnosis of GERD, and the diagnosis of refractory GERD if endoscopy is performed on optimised antisecretory therapy. While dedicated histopathological scoring of oesophageal biopsies,[81] and especially use of electron microscopy to identify dilated intercellular spaces[82] can differentiate GERD from non-GERD DGBI, routine biopsies have suboptimal performance characteristics in supporting or refuting a conclusive GERD diagnosis.[39 83] Further, the diagnostic yield of oesophageal biopsies in identifying eosinophilic oesophagitis in refractory heartburn is negligible in the absence of dysphagia or endoscopic abnormalities (0% and 1.9%, respectively), and are therefore not recommended unless there are clinical symptoms (eg, dysphagia) or endoscopic suspicion of eosinophilic oesophagitis.[84] In vivo endoscopic evaluation of oesophageal mucosal integrity was first studied using impedance electrodes incorporated into a catheter introduced through the biopsy channel of an endoscope; a second-generation device had electrode arrays mounted on an inflatable balloon to facilitate mucosal contact; neither method is currently available.[85 86] A novel endoscopic cap device that evaluates short segments of the oesophageal mucosa is under development and normative thresholds are being acquired; this has potential to identify GERD-related changes in mucosal integrity from non-GERD phenotypes at index endoscopy. Finally, a normal endoscopic examination does not rule out GERD, but identification of a hiatus hernia during endoscopy can be associated with increased reflux burden.

The updated Lyon Consensus introduces metrics for use of prolonged wireless pH monitoring (Medtronic) in unproven GERD with typical symptoms, if available and affordable.[42] Modern calibration-free wireless probes can be conveniently deployed at short notice if conclusive GERD evidence is not identified on index endoscopy performed off antisecretory therapy, and interpretation is now simplified for the average endoscopist using a concordant or dominant daily AET pattern.[41 45] A second manufacturer (Laborie) has launched a wireless pH probe. Thus, wireless pH monitoring can be a convenient option both for the patient and the operator.

The Lyon Consensus continues to support catheter-based pH-impedance for reflux monitoring, which provides accurate assessment of acidic, non-acidic and gaseous reflux episodes, of particular value when regurgitation, belching and pulmonary symptoms are being evaluated. Interpretation requires expertise, as automated interpretation may overcall or misidentify reflux episodes.[49] Catheter-based pH-impedance on therapy remains the only reflux monitoring modality that can identify refractory reflux in symptomatic proven GERD patients, and metrics are now defined.[65] Baseline impedance thresholds are now defined that conform to reliably normal, conclusively abnormal and inconclusive values, based on normative data as well as available research. However, since baseline impedance values can be abnormal in non-reflux inflammation and with fluid stasis in oesophageal hypomotility or achalasia, this parameter remains adjunctive. Conversely, PSPW may have value in phenotyping refractory GERD rather than in GERD diagnosis; further, normative thresholds are variable and calculation is cumbersome.[56 75]

High-resolution manometry (HRM) rules out achalasia spectrum disorders in PPI non-responders.[87] While HRM findings cannot diagnose GERD, abnormal EGJ morphology (ie, hiatus hernia), a compromised EGJ barrier and oesophageal hypomotility (especially using Chicago Classification 4.0 criteria) often associate with abnormal AET or erosive oesophagitis.[88–90] Hence, these HRM findings remain supportive for the diagnosis of GERD.

The Lyon Consensus endorses the concepts of unproven and proven GERD in directing evaluation of symptomatic patients. When no prior conclusive evidence of GERD exists on endoscopy or ambulatory reflux monitoring (unproven GERD), further testing seeks to determine if conclusive GERD exists, hence testing is performed off therapy (figure 2). In contrast, if prior conclusive GERD evidence exists, persisting symptoms on therapy require evaluation for refractoriness of acid or reflux burden despite management, which may include the need for escalation of therapy, endoscopic or surgical intervention. In recognition of these differences between unproven versus proven GERD, testing options and thresholds for conclusive GERD versus absence of GERD are now provided.

The Lyon Consensus evolves in concert with advances in GERD diagnosis. The utilisation of testing at index endoscopy is anticipated to grow, hence mucosal integrity assessment using an endoscopic device has potential t o direct further evaluation. Artificial intelligence will likely impact diagnostic and therapeutic paradigms within GERD, particularly in interpretation of reflux monitoring. Personalisation of management to each patient's unique presentation will help further optimise GERD diagnosis and management. Future iterations of the Lyon Consensus will attempt to keep pace with new research.

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