Gastro-oesophageal reflux disease

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Abstract | Gastro-oesophageal reflux disease (GERD) is a common disorder in adults and children. The global prevalence of GERD is high and increasing. Non-erosive reflux disease is the most common phenotype of GERD. Heartburn and regurgitation are considered classic symptoms but GERD may present with various atypical and extra-oesophageal manifestations. The pathophysiology of GERD is multifactorial and different mechanisms may result in GERD symptoms, including gastric composition and motility, anti-reflux barrier, refluxate characteristics, clearance mechanisms, mucosal integrity and symptom perception. In clinical practice, the diagnosis of GERD is commonly established on the basis of response to anti-reflux treatment; however, a more accurate diagnosis requires testing that includes upper gastrointestinal tract endoscopy and reflux monitoring. New techniques and new reflux testing parameters help to better phenotype the condition. In children, the diagnosis of GERD is primarily based on history and physical examination and treatment vary with age. Treatment in adults includes a combination of lifestyle modifications with pharmacological, endoscopic or surgical intervention. In refractory GERD, optimization of proton-pump inhibitor treatment should be attempted before a series of diagnostic tests to assess the patient's phenotype.

The Montreal consensus meeting defined gastro-oesophageal reflux disease (GERD) as a condition that develops when the reflux of stomach contents causes troublesome symptoms and/or complications[1]. In general, signs and symptoms attributed to GERD are classified as oesophageal or extra-oesophageal. Common oesophageal signs and symptoms include peptic stricture, oesophageal ulceration, Barrett oesophagus (BE), oesophageal adenocarcinoma (EAC), chest pain, water brash, belching and dysphagia[1]. Extra-oesophageal signs and symptoms are classified as laryngeal, oropharyngeal, pulmonary, cardiac, sleep-related and abdominal[1–5], demonstrating the profound effects of GERD on other organs, most in the proximity to the oesophagus (BOX 1).

Heartburn, defined as a burning sensation in the retrosternal area, and regurgitation, defined as the perception of flow of refluxed gastric content into the hypopharynx or mouth, are considered the characteristic symptoms of GERD[1]. However, heartburn is not stimulus specific and non-chemical stimuli (mechanical, thermal and electrical) can also trigger the symptom. Many upper and lower gut symptoms have been attributed to GERD. The Reflux Questionnaire (ReQuest) identified 60 different types of symptom related to GERD through physician surveys and patient groups[6]. Moreover, the same symptom reported by patients may refer to different perceptual events and different symptoms reported by patients may refer to the same perceptual event[7]. Symptoms related to GERD are considered troublesome when they adversely affect an individual's well-being. In clinical practice, patients individually determine whether they consider their symptoms as troublesome. In the general population, mild symptoms occurring ≥2 days per week or moderate-to-severe symptoms occurring >1 day per week are often considered troublesome[1,8–10].

Three phenotypic presentations of GERD exist. The most common manifestation is non-erosive reflux disease (NERD), which accounts for 60–70% of patients, followed by erosive oesophagitis (EE) (30%) and BE (6–8%) in westernized counties[11]. NERD is defined by the Montreal consensus as "the presence of troublesome reflux-associated symptoms and the absence of mucosal breaks at endoscopy", whereas the Vevey consensus defined NERD as "troublesome symptoms in the absence of oesophageal mucosal erosions/breaks at conventional endoscopy and without recent acid-suppressive therapy"[1,12,13] (BOX 2). Both definitions did not exclude the functional oesophageal disorders (FEDs) reflux hypersensitivity and functional heartburn, which are not part of the GERD spectrum; however, heartburn is a primary symptom of these FEDs as well as of all GERD phenotypes. Both FEDs are very common and account for around one-third of patients presenting with heartburn and half of those with heartburn and normal endoscopy[14].

EE is defined by the presence of visible mucosal breaks in the distal oesophagus and is considered

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a phenotypic presentation of GERD rather than a complication[1]. The severity of EE is determined using the Los Angeles classification (grade A to grade D with increasing severity)[15] and the 2017 Lyon consensus meeting suggested that grades A and B are borderline or inconclusive of GERD because of high interobserver variability on endoscopy[16]. BE, the least common phenotypic presentation of GERD, is defined as the presence of ≥1 cm of metaplastic columnar epithelium that replaces the stratified squamous epithelium that normally lines the distal oesophagus. The Prague consensus meeting developed new criteria for the endoscopic diagnosis and grading of BE[17].

NERD and EE seem to have different pathophysiological mechanisms and clinical characteristics[18–21]. In general, NERD tends not to progress and EE not to progress or regress over time[11]. Natural course assessment revealed that progression of NERD over time to primarily low grades of EE (grade A or B) is limited (~10% of the patients). Similarly, progression of EE to BE (after excluding BE underneath the inflammation) or regression of EE to NERD is limited[22]. In some patients with BE, oesophagitis may be present as well, which can mask the presence of Barrett mucosa. Importantly, neither symptom frequency, symptom severity nor both can accurately predict the underlying phenotypic presentation of GERD or severity of EE[23–26]. In addition, the same applies to distinguishing GERD phenotypes and the different FEDs that have heartburn as their predominant symptom.

Box 1 | **Atypical and extra-oesophageal signs and symptoms of GERD**

Laryngeal
Cough, laryngitis, sub-glottic stenosis, globus, laryngeal cancer, vocal cord granuloma, vocal cord irritation, vocal cord polyps and post-nasal drip

Oropharyngeal
Dental erosion, pharyngitis, sore or burning throat, gingivitis and halitosis

Ears and sinuses
Earaches, otitis media and sinusitis

Pulmonary
Chronic bronchitis, pneumonia, aspiration, bronchiectasis, asthma and idiopathic pulmonary fibrosis

Cardiac
Arrhythmia, angina and myocardial infarction

Sleep
Sleep apnoea, sleep deprivation, insomnia, snoring, nightmare and sleep disturbance

GERD, gastro-oesophageal reflux disease.

This Primer covers GERD in both adults and the paediatric population, discussing current knowledge of the different aspects of the disease, including epidemiology, pathophysiology, diagnosis, treatment and prognosis.

Epidemiology

In adults, the global prevalence of GERD is high and increasing. Data from a 2018 meta-analysis of 102 population-based studies indicate that GERD symptoms (heartburn and/or regurgitation of any severity or symptoms felt to be compatible with GERD by a clinician or according to a questionnaire)[27] are common throughout the world but vary considerably by geographical region (FIG. 1). The highest prevalence of GERD symptoms occurred in one Central American study (19.6%) whereas the lowest prevalence was observed in Asia (10.0%; 23 studies), particularly in Southeast Asia (7.4%; 18 studies). Most analysis-eligible studies were conducted in Northern Europe (31 studies) and Asia (23 studies). No studies from Africa, only one study from Central America, and few studies from South America and Australasia met the eligibility criteria. The prevalence of GERD seems to be increasing; for example, it was 45–51% higher in studies conducted after 1995 than in those conducted before 1995 (REF.[28]). Fewer data are available on the incidence of GERD, with rates of ~5 per 1,000 person-years in adults in the UK and USA[29,30]. No clear associations exist between GERD symptoms with age, sex, race or ethnicity[27,31]. For example, the pooled prevalence of GERD symptoms was slightly higher in women than in men (16.7%, 95% CI 14.9–18.6% versus 15.4%, 95% CI 13.5–17.4%, respectively)[27].

The distribution of GERD-related disorders, such as BE and EAC, varies considerably depending on sex, geographical region and race[32] (FIG. 2). More men than women are affected by BE (~70%) and EAC (~80%). Geographically, the prevalence of BE and EAC is low in East Asia and, within some regions, for example, the USA, more white individuals are affected by BE (~70%) and EAC (4–5-fold increased incidence) than are non-white individuals[32,33].

Evidence for an association between having GERD symptoms and having a genetically related family member with gastrointestinal symptoms is inconsistent[33,34]; however, several environmental factors are strongly linked to the risk of GERD symptoms. The pooled prevalence of GERD symptoms is higher in current smokers than in non-smokers (19.6%, 95% CI 14.9–24.7% versus 15.9%, 95% CI 13.1–19.0%) and slightly higher in current but not past alcohol drinkers than in non-drinkers (20.3%, 95% CI 13.6–28.0% versus 18.1%, 95% CI 14.3–22.3%)[27]. The prevalence of GERD symptoms in non-steroidal anti-inflammatory drug users is significantly higher than in non-users (25.5%, 95% CI 18.4–33.3% versus 19.6%, 95% CI 14.5–25.1%; OR 1.44, 95% CI 1.10–1.88). In addition, the prevalence is higher in those with low income than in those with medium or high income. A similar trend is seen for education with a higher prevalence in those with low (primary school or less) educational level than in those with medium (secondary or high school) educational level (OR 1.47, 95% CI 1.25–1.73) or high educational level (OR 1.78, 95% CI 1.39–2.28)[27].

GERD has been positively associated with increased consumption of fat, sweets, chocolate, and salt and inversely associated with consumption of fruit and fibre; however, evidence for a causal association between long-term dietary patterns independent of obesity is scarce and inconsistent[35–37]. For example, a cross-sectional study reported that a high dietary fat intake was associated with an increased risk of GERD symptoms and EE, whereas a high fibre intake correlated with a reduced risk of GERD symptoms[35]. By contrast, in a study in monozygotic twins, none of the studied dietary items (vegetables, fruit, fish, meat, rice, flour-based foods, milk, sandwiches, potatoes, and grilled and fried food) was associated with a risk of frequent GERD symptoms[38]. A systematic review based on observational studies showed no evidence of carbonated beverages promoting GERD[39]. Small randomized controlled trials showed more pH-verified supine reflux after a late evening meal[40] and an increased number of days without heartburn and reduced severity score with the intake of a dietary fibre product[41]. More data exist for BE and EAC and an inverse association with intake of vitamin C, β-carotene, fruit and vegetables (especially dark green, leafy and cruciferous vegetables), carbohydrates, fibre, and iron[42].

The relationship between physical activity and GERD is complex. Moderate, regular aerobic exercise has been inversely associated with GERD symptoms[37,43]. By contrast, physical activity at work, for example, in a stooped posture, and strenuous exercise, such as bicycle riding, weight lifting and swimming, are positively associated with the presence of GERD symptoms, particularly during or shortly after the activity[38,43].

Obesity is a strong risk factor for GERD and the rising prevalence of obesity might explain some of the increase in prevalence of GERD symptoms and incidence of GERD-related complications. The pooled prevalence is higher in individuals with obesity than in those without (22.1%, 95% CI 17.4–27.2% versus 14.2%, 95% CI 10.8–18.0%; OR 1.73, 95% CI 1.46–2.06)[27]. Waist circumference and waist-to-hip ratio correlate more strongly than body mass index with the risk of GERD symptoms, EE, BE and EAC. In a meta-analysis of observational studies, individuals with central adiposity had a higher risk of EE (OR 1.87, 95% CI 1.51–2.31) and BE (OR 1.98, 95% CI 1.52–2.57) than those without[44]. Abdominal obesity promotes GERD by elevating intra-abdominal pressure, which promotes reflux and the development of hiatal hernia[45]. Studies comparing CT-measured abdominal fat composition found that patients with EE and BE have greater intra-abdominal visceral adiposity than individuals in a control population[46]. Obesity prevalence is increasing in most regions in which GERD prevalence is increasing, obesity is more common in men than in women, and abdominal obesity is more likely in men than in women and in white individuals than in Black individuals[47]. Some of the effect of obesity on GERD might be confounded by associated differences in diet or physical activity, but studies that adjusted for these factors did not show a meaningful extent of confounding and obesity remained an independent risk factor for GERD.

No consistent association between the presence or treatment of *Helicobacter pylori* and GERD symptoms has been found. A meta-analysis of trials of *H. pylori* eradication found that the risk of GERD symptoms was not increased after eradication of *H. pylori*[48]. In clinical trials, *H. pylori* eradication has not been consistently associated with the development of new GERD but may lead to the development of new EE[49]. Eradication of *H. pylori* does not seem to affect the healing rates or relapse rates of pre-existing GERD. However, pooled data suggest *H. pylori* as a possible preventive factor (that is, inverse association) for EE, BE and EAC[50,51]. This effect is attributed to decreased acid production, resulting from corpus gastritis or gastric atrophy, leading to decreased oesophageal exposure to acid[52,53]. *H. pylori* infection also offers a partial explanation for the observed trends in GERD epidemiology: the infection is common in regions with low BE and EAC prevalence and in racial groups (for example, Black individuals) less likely to develop these conditions.

GERD has been linked to several extra-oesophageal symptoms and disorders (for example, asthma, chronic obstructive pulmonary disease, interstitial lung disease and sleep apnoea) but the direction of causality is unclear[54,55]. The overall odds ratio for studies reporting the prevalence of GERD symptoms in individuals with asthma was 5.5 (95% CI 1.9–15.8) and for studies measuring the prevalence of asthma in GERD it was 2.3 (95% CI 1.8–2.8). The evidence on the temporal association is mixed[56].

GERD is common in infants and children. Population studies show that 70% of children from birth to age 5 years present with a main complaint of GERD for ≥1 visit and 25% present for ≥3 visits for GERD complaints[57]. In no age group is gastro-oesophageal reflux more apparent than in infancy. Infants visibly regurgitate throughout the first year of life with the peak age for visible regurgitation between 4 and 6 months of age[58]. Regurgitation, although common, is not considered pathologic unless the refluxate is accompanied by bothersome symptoms, including feeding difficulties, crying, back arching and poor growth[59]. Unfortunately, these symptoms are common in up to 40% of healthy infants, so proving that they are, in fact, reflux-related rather than normal infant behaviour or related to colic or cow milk protein intolerance is difficult[60]. In general, rates of visible regurgitation and other reflux symptoms decline after 6 months of age, which coincides with the introduction of solid food and the acquisition of developmental milestones such as sitting upright, both of which may contribute to symptomatic improvement[58].

Box 2 | GERD Experts Consensus Meetings

- Los Angeles — consensus meeting on endoscopic classification of erosive oesophagitis[15]
- Lyon — consensus meeting on diagnostic metrics for GERD[16]
- Montreal — consensus meeting on GERD[1]
- Prague — consensus meeting on Barrett oesophagus[17]
- Vevey — consensus meeting on non-erosive reflux disease[13]

GERD, gastro-oesophageal reflux disease.

Hiatal hernia
The sliding of the upper part of the stomach into the chest through the diaphragmatic hiatus.

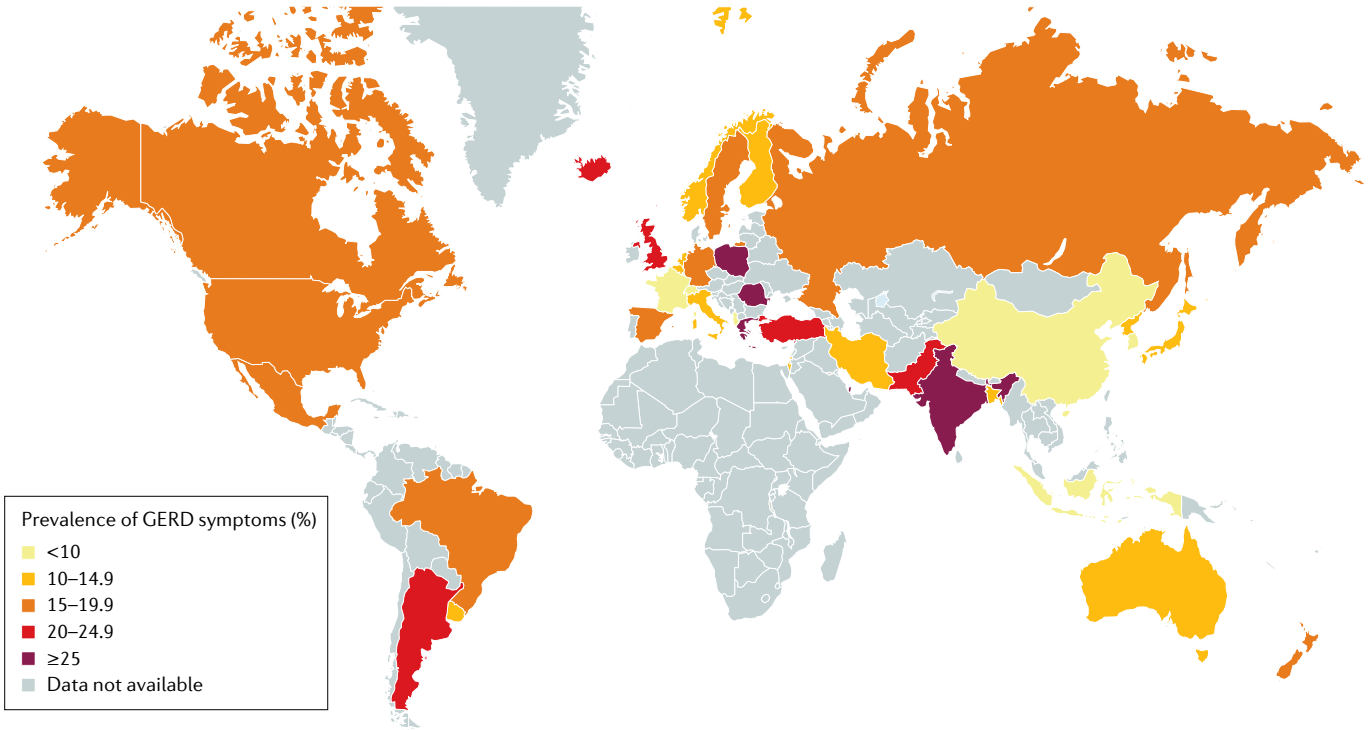

Fig. 1 | **Global distribution of the burden of GERD.** Sample-size weighted mean estimates of the prevalence of at least weekly heartburn and/or regurgitation. GERD, gastro-oesophageal reflux disease. Reprinted with permission from REF.[27], BMJ Publishing.

The incidence of GERD is high in infancy, but a second peak occurs during the school-age years, when children present with more typical symptoms such as heartburn, chest pain and epigastric pain[57,61].

Few studies examined the clinical course of GERD in children without comorbid neurological deficits or congenital oesophageal anomalies and reported that a large proportion of patients continue to have GERD symptoms and signs and use anti-secretory medications[62]. One cohort study in 113 individuals with childhood GERD reported that 65.5% of the study sample had monthly GERD symptoms, 46% had weekly symptoms and 16.8% with no weekly symptoms were using proton-pump inhibitors (PPIs).

Mechanisms/pathophysiology

The pathophysiology of GERD is multifactorial, including the gastric acid pocket, abnormal gastric emptying, and failure of the anti-reflux barrier and crural diaphragm (CD). In addition, refluxate characteristics and oesophageal clearance mechanisms affect the extent of mucosal damage. Furthermore, mucosal integrity along with peripheral, central and psychological mechanisms are critical for symptom perception (FIG. 3).

Gastric factors

As a group, patients with GERD do not have a substantial increase in gastric acid secretion[63]. Perhaps more important than total gastric acid content is its location relative to the oesophagogastric junction. Studies have shown an area of highly acidic gastric juice below the oesophagogastric junction[64], which is not affected by the buffering effect of meals and has been named the acid pocket[65]. This area is the source of postprandial acid reflux. The pocket extends for 2–3 cm and involves the cardia across the squamocolumnar junction. In patients with GERD, it extends higher up into the lower oesophageal sphincter (LES) and distal oesophagus (up to 6 cm above the squamocolumnar junction), especially in those with large hiatal hernias[66–68].

Only 30% of patients with GERD have abnormal gastric emptying[69]. However, delayed gastric emptying may modify postprandial reflux. A disturbed gastric accommodation to a meal and prolonged postprandial fundic relaxation have been described in patients with GERD[70,71]. Furthermore, the gastric emptying rate can determine the proximal extent of the gastro-oesophageal refluxate[71]. The increased residual gastric volume after a meal can underlie postprandial reflux episodes with a higher proximal extent and consequent extra-oesophageal or respiratory symptoms secondary to GERD.

Anti-reflux barrier

The anti-reflux barrier is a high-pressure zone between the stomach and the oesophagus mainly composed of the LES, the CD and the gastro-oesophageal flap valve, which is supported by the phrenoesophageal ligament and the gastric sling fibres of the gastric cardia (FIG. 3).

Gastro-oesophageal reflux usually occurs through transient LES relaxations (TLESRs), low LES pressure (LESP), swallow-associated LES relaxations and straining during periods with low LES pressure. Patients with

Transient LES relaxations (TLESRs). The sudden relaxation of the lower oesophageal sphincter (LES) that is not preceded by a swallow; a normal gastric venting mechanism that is the most common cause of gastro-oesophageal reflux.

Bilitec
A 24-hour intra-luminal catheter that records the frequency and duration of bile exposure in the oesophagus by using bilirubin as a surrogate marker for bile (currently not available for clinical use).

oesophagitis have a lower mean basal LESP than individuals with other GERD phenotypes or without GERD[72]. The TLESR is an LES relaxation that is not induced by swallowing. It is accompanied by diaphragmatic inhibition and substantial oesophageal shortening (owing to contraction of the longitudinal muscle layer) and persists for longer periods than swallow-induced LES relaxations (>10 seconds)[73,74]. Most TLESRs occur in the first 2 hours after a meal. The rate of TLESRs is similar in healthy individuals and patients with GERD[75,76]. However, in healthy individuals, only 30% of TLESRs are accompanied by acid reflux compared with 65% in patients with GERD. In healthy individuals and patients with mild oesophagitis, most reflux episodes occur during TLESRs[77–79]. In those with more severe reflux oesophagitis and those with hiatal hernia, a greater proportion of reflux occurs during absent basal LES pressure and swallow-induced LES relaxations[80,81].

The LES and CD are anatomically superimposed in the absence of a hiatal hernia. Under conditions of very low LESP, gastro-oesophageal reflux occurs only if the activity of the CD is inhibited[73]. The CD is an effective barrier against reflux, particularly during considerable increases in intragastric pressure such as cough or straining. During TLESRs, the LES is relaxed but reflux occurs only when the CD stops contraction. This neural inhibition of CD activity is part of the TLESR mechanism. A hiatal hernia separates the LES from the CD and predisposes to GERD by weakening the gastro-oesophageal barrier. The CD suffers axial displacement and radial disruption owing to atrophy secondary to dilatation of the hiatus[82,83]. Patients with hiatal hernia may have impaired oesophageal acid clearance owing to a mechanism of re-reflux during swallowing, that is, early retrograde flow from the hiatal sac to the oesophagus immediately after LES relaxation[84].

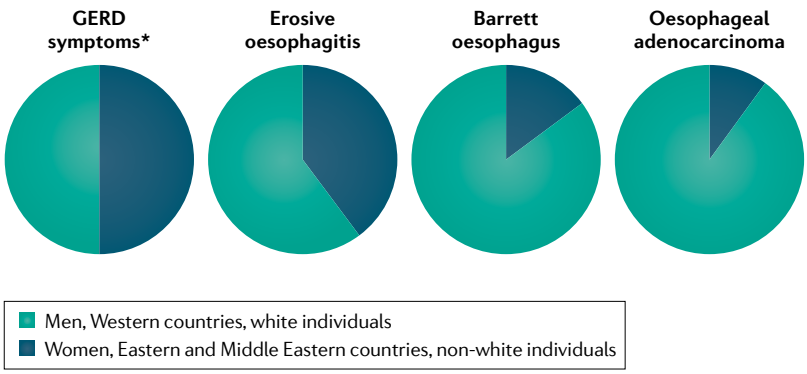

Fig. 2 | **Epidemiological trends in GERD-related disorders.** Typical gastro-oesophageal reflux disease (GERD) symptoms are mostly balanced between comparator groups according to sex, geographical region and race; however, the distribution of GERD-related complications becomes progressively skewed according to severity of the complication. Erosive oesophagitis, Barrett oesophagus and oesophageal adenocarcinoma affect more men than women, more individuals in Western countries (such as North America and Western Europe) than other regions, and more white individuals than non-white individuals. The proportions in all circles are schematic and neither reflect specific data points nor exact equivalence among sex, race or geographical subgroups. *GERD symptoms are similar between Western and Middle Eastern countries but are lower in Southeast Asian countries. Adapted with permission from REF.[32], BMJ Publishing.

Refluxate characteristics

Acid reflux. Acid reflux is considered when the pH of the refluxate is <4. Compared with healthy individuals, patients with GERD have a higher rate and proportion of acid reflux and a higher proportion of acid pure-liquid reflux (without gas). Increasing levels of oesophageal acid exposure correlate with increasing severity of oesophageal mucosal damage[85–87]. Heartburn and regurgitation are more likely to be evoked when the pH drop is large, the proximal extent of the refluxate is high, and the volume clearance and acid clearance are delayed. Furthermore, sensitization of the oesophagus occurs by preceding acid reflux events[88].

Weakly acidic reflux. Weakly acidic or non-acid reflux can elicit symptoms, particularly regurgitation, in patients with typical GERD symptoms using a PPI and, less frequently, heartburn or chest pain[89]. Weakly acidic reflux might also be involved in persistent mucosal damage in patients with BE and in those with oesophagitis not responding to a double dose of PPI treatment. This type of refluxate can also be associated with microaspiration in respiratory disorders in both adults and children[90–96]. Furthermore, weakly acidic reflux is the almost unique type of refluxate in young babies with frequent feeding[97,98]. Weakly acidic reflux is not synonymous with bile reflux.

Bile reflux. Gastric contents include bile acids such as cholic and deoxycholic acids. Studies using pH and Bilitec monitoring have shown that most bile reflux events occur in an acid reflux setting[99,100]. In addition, the severity of both acid and duodenogastro-oesophageal reflux (including bile reflux) gradually increase from healthy individuals to patients with oesophagitis with the highest values observed in patients with BE[101]. Perfusions of non-acidic solutions containing bile acids were found to provoke heartburn[102]. Furthermore, exposure of rabbit oesophageal mucosa to weakly acidic solutions containing bile acids increased mucosal permeability and induced dilated intercellular spaces (DIS), constituting a proposed histopathological mechanism necessary for the sensation of heartburn[103]. The relationship between bile reflux and the persistence of GERD symptoms despite PPI treatment remains controversial. One study suggested a role for bile reflux in patients with refractory symptoms[104]; however, in another study, abnormal bile reflux was documented in 82% of patients who respond to PPI therapy compared with 67% of those who do not[105]. A study from 2020 associated this type of bile reflux not only with oesophageal mucosal injury but also with symptom development, which is relevant to explain refractoriness to PPI treatment[106].

Gas reflux. The presence of gas in the refluxate increases the perception of reflux events[107,108]. Supragastric belching, air that enters and leaves the oesophagus rapidly without reaching the stomach, is commonly detected in patients with GERD symptoms[109] and is mechanistically associated with increased acid reflux in some of these patients[110]. Gastric belching occurs during TLESRs and is frequently associated with liquid acid or non-acid reflux[111].

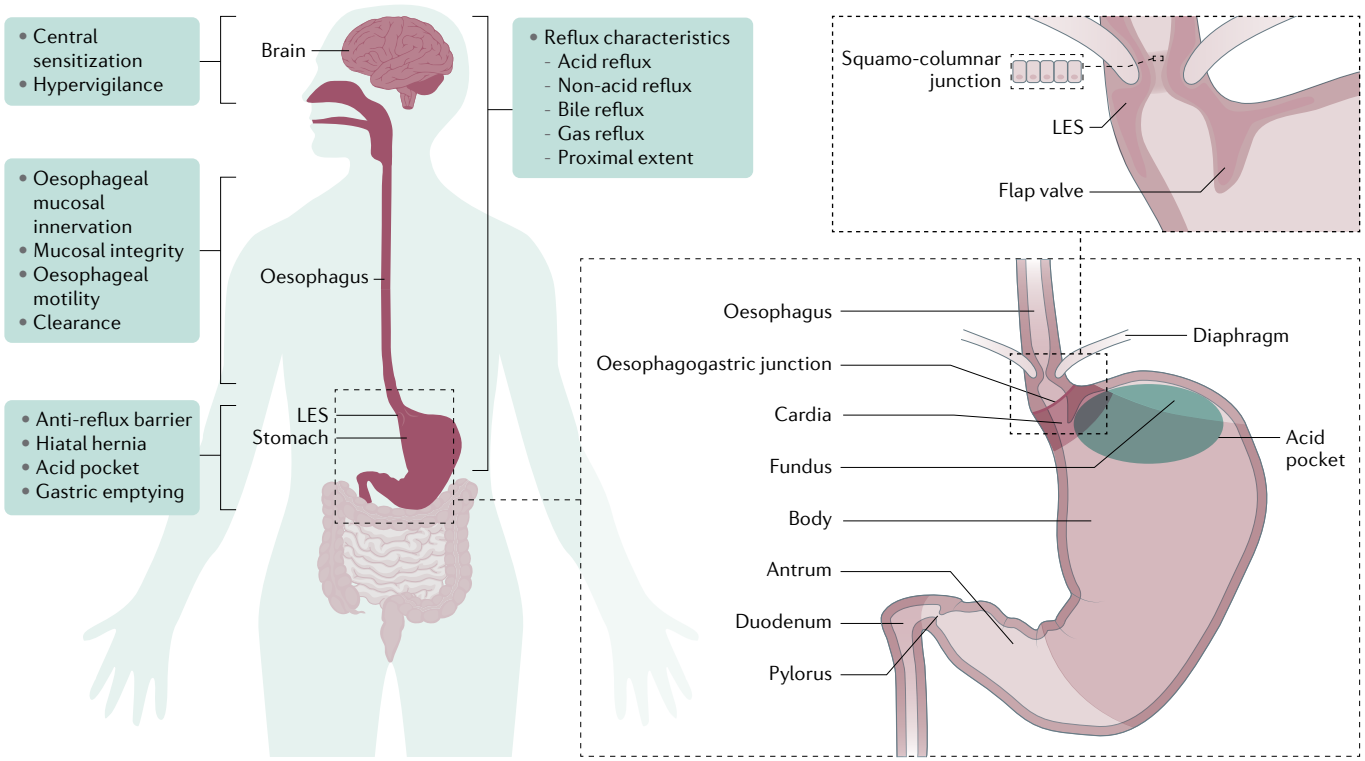

Fig. 3 | **Mechanisms of symptom and mucosal injury generation in GERD.** Several mechanisms can be involved in symptom generation and the development of oesophageal mucosal injury in patients with gastro-oesophageal reflux disease (GERD). They include central nervous system, oesophageal and gastric mechanisms that can affect or interact with each other. Not all shown mechanisms are required for GERD development. Thus, patients may harbour different mechanisms leading to GERD, resulting in a wide array of disease manifestations. LES, lower oesophageal sphincter.

Volume, proximal extent and oesophageal distension

Indirect indicators of reflux volume are the proximal extent of the pH or impedance changes. Studies using pH-metry with multiple sensors or pH–impedance measurement have shown that symptomatic reflux episodes reached a higher proximal extent than asymptomatic reflux events[112–114]. Reflux episodes associated with regurgitation had a higher proximal extent than reflux episodes associated with heartburn[88]. Reflux-induced oesophageal distension has been suggested to be critical for symptom perception, particularly in patients with refractory GERD[115,116].

Oesophageal clearance

The duration of exposure of the oesophageal mucosa to the refluxate depends on the effectiveness of reflux clearance mechanisms (peristalsis and salivation) and the presence of a hiatal hernia. The clearance process involves a rapid initial volume clearance by peristalsis followed by a stepwise chemical clearance by the arrival of bicarbonate-rich saliva and subsequent swallows[117].

Volume clearance and oesophageal motility. Effective swallow-induced primary peristalsis and distension-induced secondary peristalsis are critical for volume clearance. The minimum effective contraction strength for clearance is ~30 mmHg (REF.[118]). Another relevant factor is the integrity of the peristaltic sequence. Abnormal fragmentation of peristalsis is associated with poor clearance[119,120]. The prevalence of oesophageal dysmotility ranges from 20% in patients with NERD to 48% in patients with severe oesophagitis[121–123]. Secondary peristalsis is more important during sleep when the rate of swallowing is reduced and is impaired in patients with GERD with and without oesophagitis[124]. Gastro-oesophageal reflux events are immediately followed by a reflex that triggers swallow-induced peristalsis and/or secondary peristalsis.

Oesophageal emptying and clearance can be affected by the presence of a hiatal hernia. Studies using scintigraphic, radiologic and pH–impedance assessment have described the phenomenon of re-reflux, which is the reflux of liquid from the hernial sac during swallowing[84,125,126].

Chemical clearance. After initial volume clearance by peristalsis, the distal oesophageal mucosa remains acidic. Subsequent swallows contribute saliva rich in bicarbonate, which neutralizes the acidic milieu[117]. Pharyngeal pumping and proximal oesophageal contractions are sufficient to bring saliva to the distal oesophagus both in upright and supine positions[127]. Connective tissue disorders, such as scleroderma, or chronic xerostomia (dry mouth) and Sjögren syndrome are associated with prolonged oesophageal chemical clearance and GERD[128,129]. Furthermore, age-related or pharmacological reduction of salivary secretion can contribute to reflux disease in elderly patients[130]. Oesophageal chemical clearance has been assessed during reflux monitoring analysis using a parameter called post-reflux

Pharyngeal pumping
A rhythmic contraction (pumping) of the pharynx in response to the presence of a food bolus.

Sjögren syndrome
An autoimmune inflammatory disorder characterized by xerophthalmia (dry eyes) and xerostomia (dry mouth).

swallow-induced peristaltic wave, a reflex triggered by a reflux episode that induces saliva secretion and swallowing and suggested to be impaired in patients with GERD and patients refractory to PPI treatment[131,132].

Oesophageal mucosa

When the refluxate reaches the oesophagus and clearance mechanisms fail, the oesophageal mucosa is exposed to gastric contents. The extent of exposure and the strength and characteristics of mucosal defensive mechanisms determines the severity of reflux-induced mucosal damage.

Oesophagitis. One-third of patients having reflux symptoms, such as heartburn or regurgitation, have endoscopic findings of mucosal inflammation, that is, oesophagitis. Reflux oesophagitis is defined endoscopically by visible breaks in the distal oesophageal mucosa. Mechanisms underlying the most frequent GERD symptom — heartburn — remain incompletely understood. Patients with erosive reflux disease have endoscopically visible defects in the mucosa, allowing noxious reflux contents to permeate into the inflamed and damaged oesophageal wall, which is likely to activate sensory afferent nerves present in deeper epithelium resulting in the perception of heartburn. However, most patients with GERD have a macroscopically normal oesophageal mucosa and are diagnosed with NERD. In these patients, the mechanism for heartburn pathogenesis is less clear. In recent years, hypotheses for heartburn perception in NERD have predominantly focused on evidence that the mucosa, although macroscopically normal, displays microscopic and functional barrier defects. In NERD, electron microscopy revealed DIS[133] and oesophageal mucosa of patients with NERD displays functional evidence of increased permeability. DIS is most prominently seen in the basal layers of the epithelium.

Studies in the past decade suggested the hypothesis that refluxed gastric juice stimulates the epithelium to secrete pro-inflammatory cytokines that induce epithelial proliferative changes and attract T lymphocytes and other inflammatory cells that ultimately damage the mucosa[134–136]. Sensory nerve endings that reach the oesophageal mucosa and express acid-sensing ion channels are activated by cytokine-induced inflammation as well as by deep nerves of the papillae, which become directly activated by pro-inflammatory cytokines[137] (FIG. 4).

NERD. Typical reflux symptoms may occur in the presence or absence of oesophagitis. NERD is the most common phenotype of GERD[138]. The oesophageal mucosa in patients with NERD does not show oesophagitis but is also not completely normal. In NERD, the basal layer of oesophageal mucosal epithelium demonstrates DIS[133]. This abnormality is related to mucosal exposure

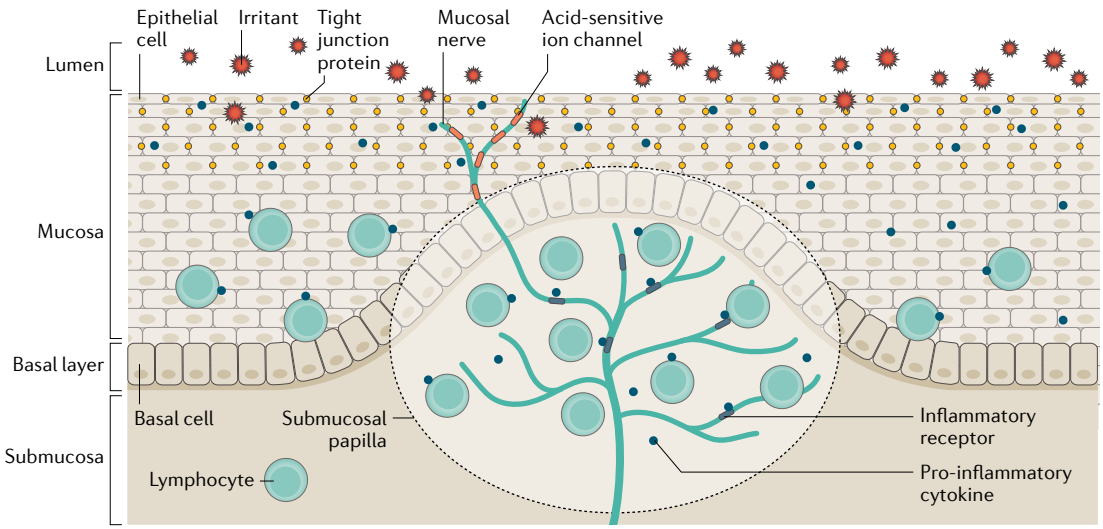

Fig. 4 | **Possible integrated model of mucosal pathogenesis in GERD oesophageal injury and symptoms.** Mucosal pathogenesis in gastro-oesophageal reflux disease (GERD) might involve multiple factors, including the integrity of the epithelial barrier, the presence of acid-sensitive receptors in epithelial cells and nerves, and mucosal inflammation, which play overlapping and interdependent roles in the pathogenesis of oesophageal pain and sensitivity. Contact of the mucosa with irritants, for example, acid, pepsin or bile acids, in the refluxate triggers the secretion of inflammatory mediators, such as IL8, IL-1β and TNF, by oesophageal epithelial cells. These are likely to directly activate or heighten the sensitization of peripheral afferent nerves as seen in animal studies of colonic tissue, where previously silent visceral afferent nerves are activated by chemical and inflammatory mediators leading to continuous neuronal firing. Tight junctions are critical components of the intercellular barrier and defective tight junctions are responsible for the dilation of intercellular spaces. Increased permeability due to the dilation of intercellular spaces increases the penetration of luminal irritants. Cytokine secretion triggers the infiltration of lymphocytes from the submucosal space into the oesophageal epithelium. Acid-sensitive ion channels in the sensory nerve endings and epithelial cells in the oesophageal mucosa can be activated by both luminal acid that has penetrated and the acidic microenvironment induced by cytokine-mediated inflammation. In addition, nerves in submucosal papillae can be activated by pro-inflammatory cytokines. Activated nociceptive nerves can release calcitonin gene-related peptide and substance P, causing pain even in the absence of endoscopically visualized macroscopic mucosal injury. Adapted from REF.[137], CC BY 4.0.

to acid as it frequently resolves with PPI therapy[139]. Furthermore, microscopic inflammation with neutrophil and eosinophilic infiltration is frequently observed in biopsy samples from patients with NERD.

Alterations of mucosal integrity can be assessed in vivo by measuring mucosal impedance either during reflux monitoring with pH–impedance measurement or using an endoscopic mucosal impedance technique. In the absence of swallows or reflux, measurement of mucosal baseline impedance provides an idea of the integrity or alteration of mucosal permeability. Patients with NERD have lower baseline mucosal impedance than healthy individuals and patients with functional heartburn and a greater sensitivity to acid is observed in patients with lower baseline impedance[140,141].

Oesophageal sensitivity and mucosal innervation. Oesophageal sensitivity can modulate the perception of symptoms. Patients may have increased sensitivity to the presence of acid or mechanical distension. They can have increased sensitivity to experimental stimulations or to their own reflux episodes. The perfusion of acid into the oesophagus can produce heartburn[84]. In many patients with GERD, a temporal relationship between acid reflux episodes and heartburn is found[113,142]. Both spinal and vagal afferent fibres are important in visceral nociception[143,144]. Some patients with reflux symptoms have normal oesophageal acid exposure but perceive their few physiological reflux episodes very intensively. This condition has been called acid-sensitive oesophagus (reflux hypersensitivity)[145].

Afferent fibres projecting to the oesophagus can be excited by the presence of acid[146]. Indeed, vagal and spinal afferent nerves express cation channels that act as molecular acid sensors. Several receptors (acid-sensitive ion channels) modulate oesophageal sensitivity to acid[147]. Transient receptor potential vanilloid receptors are also important in acid-induced oesophageal nociception[148]. P2X2-containing purinoceptors are sensitized by acid in the presence of ATP[149]. The activation of proteinase-activated receptor 2 (PAR2) sensitizes cultured human oesophageal epithelial cells to acid. PAR2 can be activated during the micro-inflammatory process and/or by enzymes, such as trypsin, during reflux, which might sensitize sensory afferent nerves.

Oesophageal hypersensitivity may be due to peripheral sensitization, central sensitization or a combination of both[150]. In peripheral sensitization, there is a decreased threshold for and an increased magnitude of the sensory response to a stimulus, which is usually influenced by inflammation. Peripheral sensitization can be rapid and short-lasting but prolonged or repetitive injury or inflammation can affect gene expression levels, which leads to prolonged peripheral sensitization[150]. Repetitive firing of nociceptive signals from the periphery can alter the central processing of visceral sensory information[151]. This central sensitization may contribute to visceral hypersensitivity in the oesophagus. Patients with NERD have not only increased sensitivity of the oesophagus[152] but also increased somatic sensitivity of the chest wall[153], suggesting that central sensitization is involved, at least in part, in acid and mechanosensitivity in NERD.

In the distal oesophagus, nerve fibres are located predominantly deep in the epithelium[154]. By contrast, proximal oesophageal mucosal innervation seems to be concentrated near the luminal surface. This localization is probably the reason for the heightened sensitivity of the proximal oesophagus to acid, perhaps contributing to the protective reflex mechanisms against tracheal aspiration of proximal reflux.

Recent studies have shown that patients with NERD have more superficial afferent nerves than healthy individuals or patients with EE, BE and functional heartburn both in the distal and proximal oesophagus[155]. Acid hypersensitivity in patients with NERD might be related to the increased proximity of their afferent nerves to the oesophageal lumen[156]. Oesophageal hypersensitivity is considered an important pathophysiological factor in patients with persistent symptoms despite adequate PPI treatment[157].

Psychiatric comorbidity and hypervigilance

A final component to oesophageal pain is psycho-neuro-immune modulation. Many patients with heartburn report that psychological stress worsens their symptoms. Acute experimental stress is known to reduce pain thresholds to oesophageal acid perfusion[158]. Psychosocial comorbidities also determine the severity of GERD symptoms and response to therapy[159]. Patients with GERD have increased sensitivity to acid perfusion after a night of sleep deprivation[160]. Although this is likely to be, at least in part, a central phenomenon, it is interesting to note that acute stress induced oesophageal mucosal changes owing to DIS in rats[161].

Oesophageal hypervigilance is a phenomenon comprising cognitive and affective processes, such as specific attention to oesophageal sensations, increased anxiety about symptoms and expected pain, and catastrophic thoughts about symptom consequences[159]. One study found that oesophageal hypervigilance persists among patients regardless of acid burden and symptom index and predicts symptom severity[159,162].

Several studies have indicated an overlap between GERD and various functional gastrointestinal disorders. The overlapping conditions reported have mainly been FEDs, functional dyspepsia and irritable bowel syndrome. The available literature is frequently based on symptomatic questionnaires or endoscopic procedures to diagnose GERD. The pathophysiological mechanism that explains the overlap is not completely understood. Visceral hypersensitivity, minimal abnormalities of motility, and peripheral and central neural alterations have been proposed as common pathophysiological mechanisms among GERD and functional gastrointestinal disorders[163].

Paediatric population

As in adults, the primary mechanism of gastro-oesophageal reflux in children is TLESR. Studies in infants and children have shown that TLESRs account for ≥70% of reflux events and the remaining events occur when there is evidence of a hypotonic LES or in patients with elevations in gastric pressure relative to LES pressures. In infants with elevations in gastric pressure,

Box 3 | **GERD that is not responsive to standard PPI therapy**

Mechanisms of PPI-refractory GERD

- Residual reflux (acidic, weakly acidic or weakly alkaline)
- Poor compliance
- Improper dosing time of PPI
- Overlap with functional heartburn or reflux hypersensitivity
- Overlap with functional dyspepsia or irritable bowel syndrome
- Psychological comorbidity
- Bile acid reflux
- Delayed gastric emptying
- Reduced PPI bioavailability
- Rapid PPI metabolism
- Major oesophageal motor disorder
- Large hiatal hernia
- Post sleeve gastrectomy
- Post peroral oesophageal myotomy

Optimization of PPI treatment in patients with refractory GERD

- Ensure compliance with lifestyle modifications
- Initiate night-time precautions, such as elevating the head of the bead, avoiding eating at least 3 hours before bedtime, avoiding the right decubitus position
- Assess compliance with PPI therapy
- Evaluate proper dosing time of PPI (30–45 minutes before a meal)
- Split or spread the PPI dose (morning and evening)
- Consider adding an H2RA, an alginate-based treatment, baclofen or a prokinetic
- Address psychological comorbidity

GERD, gastro-oesophageal reflux disease; H2RA, histamine 2 receptor antagonist; PPI, proton-pump inhibitor.

Angle of His
The acute angle created between the cardia at the entrance to the stomach and the oesophagus.

Gastroparesis
A neuromuscular disorder of the stomach that is characterized by delayed solid food emptying in the absence of mechanical obstruction.

Eosinophilic oesophagitis
A chronic immune-antigen-mediated oesophageal disorder, characterized by symptoms related to oesophageal dysfunction and, histologically, by eosinophil-predominant inflammation.

Pill-induced injury
Oesophageal injury due to direct damage to the oesophageal mucosa by a pill.

pH–impedance monitoring
Detection of both acid and non-acid gastro-oesophageal reflux episodes with multichannel intra-oesophageal catheter by measuring intra-luminal changes in pH and impedance.

retrograde bolus flow can occur even with pressures as low as 5–30 mmHg (REFS[164,165]). Congenital anomalies or diseases that result from an absence of normal physiological protective mechanisms, such as LES tone, diaphragmatic reinforcement and an intact angle of His, can also cause gastro-oesophageal reflux in children. Patients with a congenital diaphragmatic hernia, oesophageal atresia with or without hiatal hernia, and patients who have had gastric surgeries are at the highest risk[166,167]. Finally, although not a primary mechanism of reflux, oesophageal stasis from impaired oesophageal motility in children with oesophageal atresia, achalasia and connective tissue disorders results in poor reflux clearance. These patients might not have more reflux episodes but their reflux clearance is poor and results in both oesophageal and respiratory complications from oesophageal pooling of both food and reflux[166,168,169].

Diagnosis, screening and prevention

GERD is commonly diagnosed based either on the response of suspected reflux-related symptoms to empiric acid-suppressive therapy or on objective findings by diagnostic tests. However, diagnostic tests are neither sensitive (30–76%) nor specific (62–96%) enough by themselves to enable a definitive diagnosis of GERD[170,171]. Reflux disease is identified in only 54% of patients with heartburn and in only 29% with regurgitation[172] because symptoms of heartburn and regurgitation are common among non-GERD conditions, such as gastroparesis, FEDs or functional dyspepsia and eosinophilic oesophagitis. Extra-oesophageal symptoms attributed to reflux disease have even lower sensitivity for GERD diagnosis. The Reflux Disease Questionnaire (RDQ) and the Gastro-oesophageal reflux disease Questionnaire (GerdQ), which are useful research tools in assessing for GERD, have similar limitations to physiological tests. Thus, the response to acid-suppressive therapy (PPI test) is often employed to suggest an association between symptoms and GERD. Diagnostic tests in adults with suspected GERD are reserved for those who continue to be symptomatic despite aggressive acid-suppressive therapy or in those who have established GERD but require surgical intervention.

In patients who continue to have symptoms despite PPI therapy, the role of reflux in ongoing symptoms is an important indication for diagnostic testing (BOX 3). GERD diagnostic tests either assess for the presence of visual alterations in the oesophageal mucosa (oesophagitis or BE) or employ devices (capsule or catheter) to determine the presence and extent of gastro-oesophageal reflux. However, the nuances of which tests to use and how to conduct these tests continue to challenge gastroenterologists. Tests currently employed in diagnosing GERD in adults are shown in FIG. 5 and their characteristics are tabulated in TABLE 1.

Endoscopy and biopsies

Endoscopy is indicated in patients with chronic GERD at risk of BE (white men with a high body mass index, ≥50 years of age and with chronic GERD symptoms)[173], in those with warning symptoms (for example, dysphagia, weight loss, haematemesis and vomiting), in patients suspected of having eosinophilic oesophagitis (EoE), infection or pill-induced injury[174], and in those with suspected GERD whose symptoms do not respond to appropriate anti-secretory medical therapy. Before endoscopic or surgical anti-reflux interventions, endoscopy is a common procedure to ensure patient eligibility. The presence of oesophagitis is a strong indication that patients have GERD; however, endoscopy is normal in nearly two-thirds of untreated patients with heartburn and regurgitation. Thus, endoscopy has a high level of specificity[15] but low sensitivity for GERD[175]. Oesophageal biopsies are less commonly employed in adults with suspected GERD. In patients with normal-appearing oesophageal mucosa, the next step in diagnosing GERD is often ambulatory reflux monitoring.

Ambulatory reflux monitoring

These diagnostic tests are reserved for patients with symptoms that are refractory to PPIs and have normal endoscopy[173,176]. They include catheter-based pH monitoring, catheter-based pH–impedance monitoring and wireless pH monitoring (FIG. 5). These techniques measure reflux of acid (pH) or non-acid (impedance) material at a specified location in the distal oesophagus over a 24–96-hour period. Catheter-based tests are less costly to perform than wireless monitoring but are also less well tolerated by patients owing to discomfort with prolonged monitoring. Wireless pH monitoring, is more expensive but better tolerated and enables longer monitoring (48–96 hours), resulting in higher sensitivity for

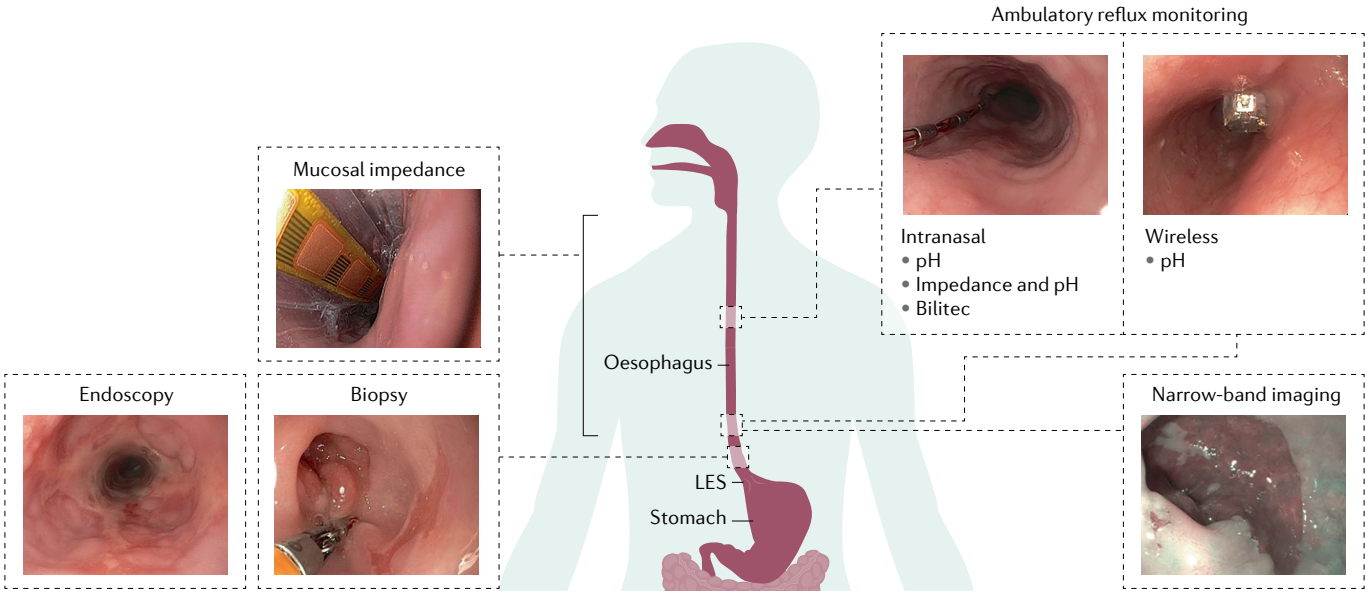

Fig. 5 | **Diagnostic strategies in GERD.** Presence of oesophagitis at endoscopy measured by the Los Angeles classification (grade A to grade D with increasing severity)[15] is sufficient to be confirmatory for gastro-oesophageal reflux disease (GERD). In those with minimal changes, narrow-band imaging may be helpful but, commonly, patients undergo oesophageal biopsy or pH testing (wireless or intranasal) to determine the degree of acid or non-acid reflux in those with persistent reflux. Mucosal integrity testing enables the measurement of mucosal impedance as a marker of reflux-induced changes in the epithelial integrity during endoscopy. In clinical practice, symptoms of heartburn and regurgitation are often enough to presume GERD, initiate empiric therapy with proton-pump inhibitors and assess for symptom improvement as a diagnostic strategy in GERD. LES, lower oesophageal sphincter.

GERD detection (TABLE 1). pH monitoring has long been employed to objectively measure the degree and extent of oesophageal acid exposure. The detection of continued acid exposure in those who continue to be symptomatic on acid-suppressive therapy may be used to assess compliance with therapy and/or alter the therapeutic strategy. Oesophageal impedance monitoring can detect the reflux of liquid and air as well as assess the proximal extent of the refluxate. pH testing is often combined with impedance monitoring to distinguish between acidic (pH <4), weakly acidic (pH 4–7) and alkaline (pH >7) reflux episodes[177–179]. Although pH–impedance measurement is an important tool for reflux detection, its value is questioned in those who are symptomatic despite acid-suppressive therapy. However, two metrics, mean nocturnal baseline impedance and post-reflux swallow-induced peristaltic wave, can be calculated from pH–impedance testing and are used to distinguish patients with heartburn and GERD from those with heartburn and a FED[132,180].

Ambulatory reflux monitoring is most often used in patients who continue to show symptoms despite aggressive acid-suppressive therapy. The technique is also employed to measure oesophageal reflux exposure in patients with negative endoscopy findings, in patients with symptoms after endoscopic or surgical reflux therapy, and to document acid control in patients with complicated GERD such as BE.

Barium studies

Fluoroscopy tracking of barium swallows is commonly performed to assess oesophageal motility and reflux. However, this technique has low sensitivity (67%) and specificity (47%) for GERD[181]. Thus, the presence or absence of reflux during barium oesophagography is not a predictor of the frequency of GERD and this diagnostic test should not be employed for GERD diagnosis by itself[182]. At this time, there is no role of scintigraphy for the diagnosis of GERD.

New techniques

Mucosal impedance. Chronic exposure of the oesophageal lumen to gastric contents results in mucosal alterations in the epithelium that may not be detectable by ambulatory prolonged reflux monitoring devices. The mucosal impedance device measures GERD by assessing the epithelial integrity through direct contact of impedance sensors with the oesophageal mucosa (FIG. 5). Initial results are promising in differentiating GERD from other oesophageal pathologies and healthy oesophagus[183–185], with a higher specificity than pH monitoring (95% versus 64%) and a higher positive predictive value (96% versus 40%)[185]. Outcome studies are needed to determine whether mucosal impedance measurement can predict response to PPI or surgery in patients with GERD.

Salivary pepsin measurement. Pepsinogen released by the gastric chief cells is converted to pepsin, which may reflux along with gastric acid to cause oesophageal symptoms or damage. Pepsin detection in the saliva has been proposed to suggest GERD and as a non-invasive method in reflux testing[186]. Despite original reports suggesting a high positive predictive value (81%) and negative predictive value (78%)[187], the use of this technology has not been widely adopted. Although early studies

suggested that salivary pepsin can diagnose GERD-related laryngeal pathology[188–191], subsequent studies[192,193] failed to show clinical benefit.

Narrow-band imaging. Narrow-band imaging (NBI) may identify small epithelial changes that suggest GERD, such as a villous mucosal surface, mucosal islands, microerosions and increased vascularity in the distal oesophagus[194]. NBI may also be employed to determine improvement of GERD after PPI therapy. However, NBI findings may not always correlate with histological analysis[194,195]. In one study in 82 patients with GERD, NBI detected small inflammatory foci in the oesophagus correlating with positive response to PPI therapy[196]. Outcome studies are needed to better understand the role of this test in GERD.

Paediatric population

GERD in children is usually diagnosed on the basis of history and physical exam alone, although reporting of symptoms is difficult in infants and young children as the symptoms, such as crying, sleep disturbance and

Table 1 | **Advantages and disadvantages of diagnostic methods for GERD**

Methods	Advantages	Disadvantages
PPI test	Good in primary care for patients without alarm symptoms	Positive in peptic ulcer disease and functional dyspepsia Specificity 24–65%
Endoscopy	Enables diagnosis of oesophagitis, BE, EoE and GERD complications Excellent specificity	Poor sensitivity 70% of patients have normal mucosa High cost but most patients undergo testing as part of the evaluation
Biopsies	Enables the diagnosis of microscopic oesophagitis and excluding EoE Normal in functional heartburn	15% of individuals with normal mucosa may have microscopic oesophagitis Requires an experienced pathologist
Catheter-based pH-metry	Easy to perform Enables detection of increased acid exposure at different locations along the oesophagus and proximal stomach Accurate automatic analysis	Unpleasant for patients, which might lead to behaviour modification Day-to-day variability Sensitivity values <71% in patients with normal endoscopy findings Requires manometry No established universal normal values
Wireless pH-metry	Enables prolonged monitoring (48–96 hours) Overcomes day-to-day variability and patients' behavioural modification Better tolerated by patients Accurate automatic analysis	Expensive Some patients have swallowing pain requiring device removal Capsule may detach prematurely, leading to inaccurate and/or suboptimal results No established universal normal values
pH–impedance	Enables detection of non-acid reflux, aerophagia and supragastric belching Enables assessment of proximal reflux Best distinction between GERD and functional heartburn	Unpleasant for patients Day-to-day variability Inaccurate automatic analysis (requires time-consuming manual editing) Requires manometry Unknown clinical relevance of non-acid reflux in the setting of aggressive acid suppression No established universal normal values
Salivary pepsin concentration	Non-invasive Detected in a high proportion of patients with GERD and in high concentrations	Moderate sensitivity and specificity Requires further validation
Mucosal impedance	Decreased in oesophagitis, NERD, BE and EoE Data acquired in short time period, eliminating the need for ambulatory tests Can measure mucosal impedance values all along oesophageal axis and radial distribution Normal in healthy individuals and functional heartburn	Requires endoscopy Liquid and air in the oesophagus may confound the results Cost unknown Undergoing validation studies
Narrow-band imaging	Distinguishes normal from NERD and reflux oesophagitis Correlates with oesophageal acid exposure	Unclear effects for patient management and/or response to treatment Not readily available in all centres

BE, Barrett oesophagus; EoE, eosinophilic oesophagitis; GERD, gastro-oesophageal reflux disease; NERD, non-erosive reflux disease; PPI, proton-pump inhibitor.

Rumination syndrome
An effortless regurgitation of undigested or partially digested food from the stomach into the mouth, followed by either re-chewing and re-swallowing or spitting of the regurgitate.

feeding difficulties, are non-specific and can have various aetiologies. As children age, the symptom reporting improves owing to the emergence of more typical symptom complaints by ≥5 years of age. In very young children, in children whose symptoms are not typical in character or severity, or in those who do not respond to conservative therapies, early testing is useful both to avoid unnecessary acid suppression therapy and to diagnose masqueraders of reflux such as rumination syndrome, EoE or FEDs[59].

Endoscopy with biopsies. Oesophagogastroduodenoscopy with biopsies is performed in the paediatric population predominantly to rule out EoE as a cause of symptoms and to assess for and treat reflux-related complications (for example, EE and strictures). In young children, EoE symptoms overlap with symptoms of gastro-oesophageal reflux; in children <5 years of age, the presenting symptoms of EoE are cough, food refusal, regurgitation, discomfort and changes in growth parameters; in older children, the EoE presenting symptoms include dysphagia, throat clearing and pain[197,198]. Because of these overlapping symptoms, endoscopy with biopsies is critical to provide a definitive diagnosis and tailor treatment appropriately. Ideally, endoscopy should be done before acid suppression therapy is initiated to provide a definitive diagnosis without masking EE or PPI-responsive EoE.

pH and/or impedance testing. Although pH-metry alone can be used in older children and adolescents to correlate typical symptoms with reflux events, pH–impedance measurement has replaced pH-metry in most infants, toddlers and early school-aged children because of the high rates of non-acid reflux in young children. In children, pH–impedance has been shown to be more sensitive in the detection of reflux events than pH probe alone[199]. Because infants and young children drink breast milk, formula, cow milk or non-dairy equivalents every 2–3 hours, gastric contents are neutralized for much of a 24-hour period and most reflux episodes are non-acidic or weakly acidic[200]. Thus, for infants or children with symptoms during or 1–2 hours after a meal, pH–impedance testing is preferred to correlate symptoms with not only acid reflux but also non-acid reflux events. Because of a lack of true paediatric normal values for pH-metry or pH–impedance (owing to the ethics of performing these tests in healthy children), the main value of the catheter-based testing lies in the ability to correlate reflux events with symptoms and not to diagnose pathologic versus non-pathologic amounts of reflux per 24-hour study. With the release of Rome IV diagnostic criteria for the diagnosis of FEDs in adults, symptom correlation is important in older children to diagnose NERD, functional heartburn and reflux hypersensitivity[201]. For extra-oesophageal symptoms, pH–impedance testing is also critical to correlate respiratory symptoms, such as cough, with reflux events; because there are no studies showing benefit of empiric acid suppression in children with respiratory symptoms, proving reflux–symptom association before treatment is important[59].

Biomarkers of extra-oesophageal reflux. Gastro-oesophageal reflux is frequently implicated as a cause of cough, wheezing, recurrent pneumonia, stridor, erythematous airways, brief resolved unexplained events, apnoea and bradycardia; however, there is mounting pH–impedance evidence that these symptoms are rarely caused by reflux events and current diagnostic algorithms recommend diagnostic testing before beginning empirical therapy for isolated respiratory symptoms[59].

Multiple studies in paediatrics have failed to show a diagnostic benefit to measuring biomarkers for extra-oesophageal symptoms; bronchoalveolar lavage lipid-laden macrophage indices and salivary, and tracheal pepsin lack the sensitivity needed to diagnose extra-oesophageal reflux disease[202–206].

High-resolution oesophageal manometry with impedance. High-resolution oesophageal manometry with impedance is not used to diagnose gastro-oesophageal reflux in children but it is a useful tool to diagnose masqueraders of reflux, such as rumination syndrome, primary motility disorders and oesophagogastric junction outflow obstruction, all of which may include regurgitation of contents from the stomach (with rumination) or oesophagus (primary motility disorders or oesophagogastric junction outflow obstruction) and this regurgitation could be misinterpreted as gastro-oesophageal reflux[207,208].

Management

Adults

Treatment of GERD in adults usually includes a combination of lifestyle modifications with pharmacological, endoscopic or surgical intervention (FIG. 6). Treatment of GERD in elderly patients (≥65 years old) is largely the same as in younger adults[209]. However, careful attention to adverse effects should be given when using histamine 2 receptor antagonists (H2RAs), specifically cimetidine, prokinetics or baclofen. Elderly patients who are good candidates for anti-reflux surgery or endoluminal endoscopic therapy are expected to have similar outcomes to younger patients[210]. For patients with refractory GERD, a more individualized therapeutic approach has been proposed but requires a series of diagnostic tests to adequately assess the refractory GERD phenotype[211].

Lifestyle modifications. Lifestyle modifications are commonly recommended as an initial therapeutic approach for patients with GERD and mild symptoms or as an addition to other therapeutic modalities in patients with moderate-to-severe symptoms. Evidence for the value of lifestyle modifications is available only for weight loss, elevation of the head of the bed and avoidance of eating at least 3 hours before bedtime[212–214]. Night-time precautions are commonly overlooked but are important in helping prevent night-time symptoms or sleep disturbances due to gastro-oesophageal reflux[215–217] (BOX 4). There is limited or no evidence for the value of other commonly recommended lifestyle modifications.

Pharmacological management. Overall, the evidence to support the value of anti-reflux medications, such as antacids, alginate, sucralfate, prokinetics and baclofen,

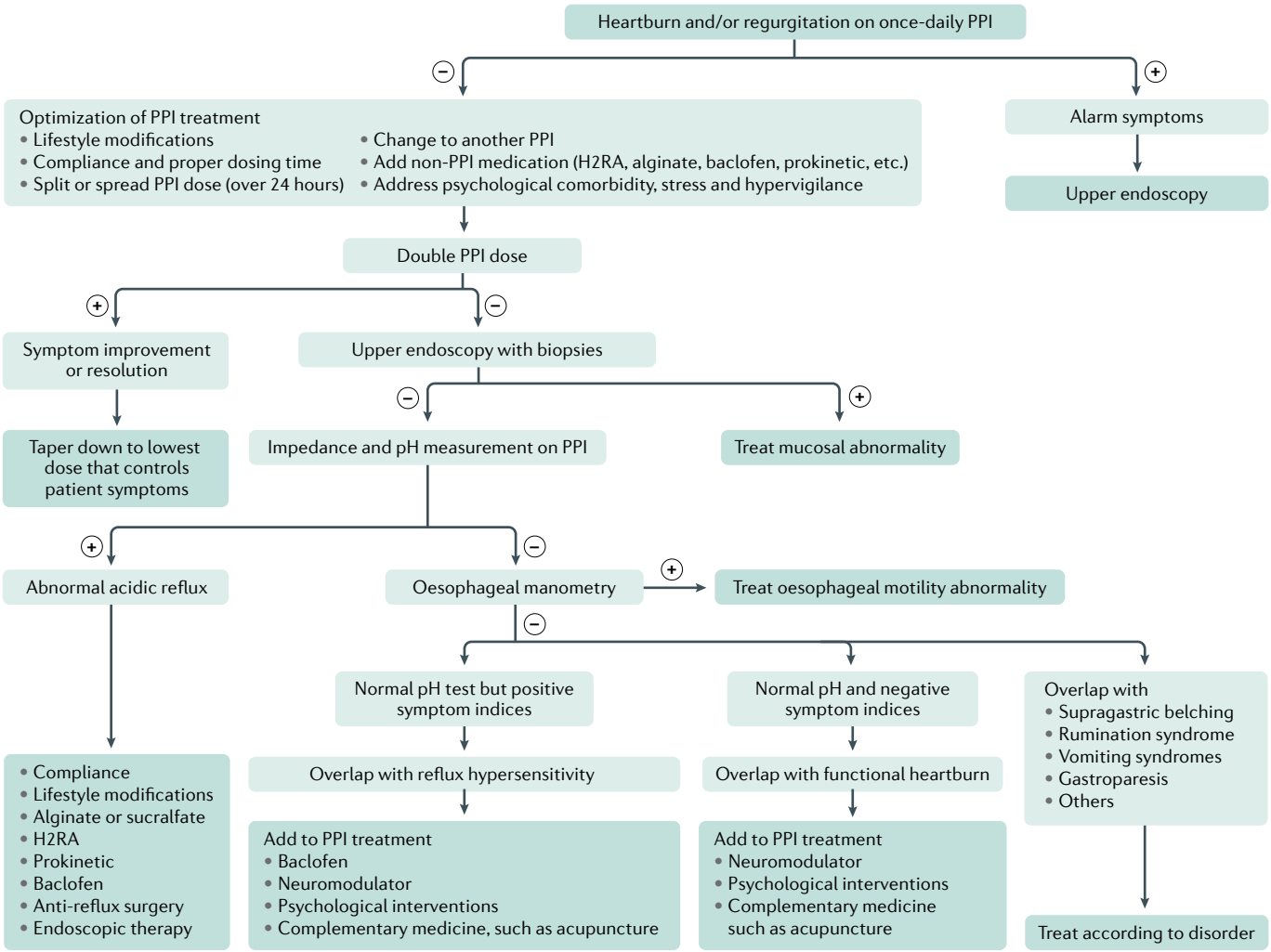

Fig. 6 | **Evaluation and management of GERD that is not responsive to PPI therapy.** Patients who demonstrate incomplete or partial response to proton-pump inhibitors (PPIs) once daily should first undergo optimization of PPI treatment. Failure to respond to PPI twice daily requires a work-up that initially involves an upper endoscopy with possible oesophageal biopsies and, subsequently, reflux testing and high-resolution oesophageal manometry. The algorithm emphasizes that, besides residual acidic reflux, several disorders may overlap with gastro-oesophageal reflux disease (GERD) and the overlapping disorders are likely to be the driving mechanism behind a patient's lack of response to PPI treatment. H2RA, histamine 2 receptor antagonist. Adapted with permission from REF.[235], Elsevier.

for the treatment of GERD and its complications is relatively limited and, for some, scarce. More robust data are available to support the efficacy of H2RAs and the various PPIs in treating patients with GERD.

Antacids have been used for decades for episodic heartburn, usually postprandial or as on-demand agents. They are basic compounds composed of different combinations of acid-neutralizing agents such as aluminium hydroxide, magnesium hydroxide, calcium carbonate, sodium citrate and sodium bicarbonate[218]. Antacids have not been shown to contribute to healing of EE or to prevent symptom recurrence or complications in patients with GERD[219,220]. These agents are relatively safe but magnesium-containing compounds can cause diarrhoea and aluminium-containing compounds can cause constipation.

Alginate is a gelatinous polysaccharide extract from brown algae that has been used in different formulations for the treatment of episodic heartburn[221]. These formulations usually contain sodium bicarbonate or potassium bicarbonate in addition to alginate. In the presence of gastric acid, they precipitate into a gel and create a foamy raft that displaces the postprandial acid pocket[222]. Alginate-based therapies are more likely to resolve GERD symptoms than placebo or antacids (OR 4.42, 95% CI 2.45–7.97)[221]. Adding alginate to once-daily PPI helped to control breakthrough symptoms in patients with GERD[223].

Sucralfate, an aluminium salt of a sulfated disaccharide, is a mucosal protectant that binds to inflamed tissue to create a protective barrier[224]. Sucralfate has been shown to be equal to H2RAs and alginate plus antacids in controlling symptoms in patients with EE and was significantly better than placebo in patients with NERD[224,225]. Sucralfate has limited effect on the healing of EE[224].

H2RAs reduce gastric acid volume and concentration by competitive inhibition of histamine at the H2 receptor

Breakthrough symptoms
Symptoms that occur while the patient is on medical therapy.

Box 4 | **Night-time precautions for GERD**

- Avoid eating at least 3 hours before bedtime
- Elevate the head of the bed
- Avoid the right decubitus position when in bed
- Turn off the lights when entering the bed
- Minimize the awake period before falling asleep
- Minimize disturbances during sleep time

GERD, gastro-oesophageal reflux disease

on the parietal cells and pepsin production by blocking the conversion of pepsinogen. Several H2RAs are approved for GERD such as cimetidine, famotidine and nizatidine. Ranitidine was recently removed from the market owing to concerns of potential association with increased risk for certain malignancies (FDA requests removal of all ranitidine products (Zantac) from the market). In equipotent doses, the different H2RAs are equivalent in acid suppression and demonstrate no significant clinical differences[226]. Studies have demonstrated that PPIs are superior to H2RAs in symptom control, mucosal healing and prevention of relapse in patients with GERD[227–229]. H2RAs could be considered in patients with NERD or in those with low-grade EE (grade A or B). However, their main appeal is their use as an on-demand therapy for patients with mild disease owing to their rapid effect on GERD symptoms, which is unsurpassed by any of the currently available PPIs. H2RAs can relieve postprandial heartburn for up to 12 hours and can prevent it if given 30 minutes before a meal[230,231]. In those who do not respond to a double dose of PPI treatment, H2RAs are commonly added at bedtime due to their suppressive effect on the night-time histamine-driven surge of gastric acid secretion[217]. Tachyphylaxis is very common and develops relatively quickly with chronic use of H2RAs, which limits their utility in clinical practice.

PPIs, such as omeprazole, lansoprazole and esomeprazole, are prodrugs that selectively concentrate in the parietal cell canaliculi, where they are activated within the acidic milieu[226]. PPIs bind covalently only to the active form of H^+/K^+ ATPase. PPIs do not have an immediate effect and are most effective when given 30–45 minutes before a meal, preferably in the morning. As PPIs have a short elimination half-life (0.5–1.5 hours), morning dosing covers meal times, which are the main precipitating factors for symptoms. PPIs suppress nocturnal, daytime and postprandial acid secretion[232,233]. PPIs have no effect on the underlying mechanisms of gastro-oesophageal reflux but alter the characteristics of reflux events from acidic to weakly acidic or weakly alkaline[234]. PPIs provide unsurpassed symptom control, EE healing and prevention of disease relapse and complications[235]. The various available PPIs differ in their pharmacokinetics and pharmacodynamics, but they demonstrate very little difference in their clinical efficacy[236]. PPIs demonstrate a dose–response effect in patients with EE but not in those with NERD[237,238]. Thus, doubling the PPI dose in patients with refractory NERD may not be an effective therapeutic strategy. Furthermore, patients with EE have a greater response to standard-dose PPI treatment in relieving heartburn symptoms than patients with NERD[238].

Chronic, long-term PPI treatment has been reported to be associated with many adverse events but the extent of causality remains to be elucidated. Overall, adverse event studies are primarily population based and not prospective and the reported risk is modest at best. Adverse effects include kidney diseases, dementia, bone fracture, myocardial infarction, small intestinal bacterial overgrowth, *Clostridium difficile* infection, pneumonia, spontaneous bacterial peritonitis and others[239]. However, a large, prospective, placebo-controlled, randomized trial published in 2019 found that pantoprazole was not associated with any adverse event when used for 3 years with the possible exception of enteric infections[240]. Current American Gastroenterological Association best practice advice recommends the use of PPIs for short-term healing, maintenance of healing and long-term symptom control[241]. Patients with uncomplicated GERD who respond should attempt to stop or reduce the dose of PPI, and any patient on long-term PPIs use should be periodically reevaluated.

Patients with GERD who do not respond to PPI once daily should undergo optimization of PPI treatment[235] (BOX 3). In those with refractory GERD (no response to twice daily PPI), a work-up is recommended to identify whether the cause is incomplete control of gastro-oesophageal reflux, an overlap with a FED (functional heartburn and reflux hypersensitivity), or other oesophageal or non-oesophageal disorders[235,242] (FIG. 6).

Several potassium-competitive acid blockers (P-CABs) are available or are in development, such as vonoprazan and tegoprazan[243]. These agents have a rapid onset of action, prolonged half-life and more profound acid inhibitory effect compared with PPIs[244]. P-CABs bind competitively and reversibly to the potassium-binding site of the proton pump. They accumulate at a much higher concentration than PPIs in the parietal cells' canaliculi and bind to both the active and inactive forms of the proton pump resulting in a faster and longer duration of the anti-secretory effect than PPIs[245]. Early onset of action is due to the rapid rise of their peak plasma concentration[246]. P-CABs have demonstrated better and earlier healing of advanced EE (grade C or D) than PPIs[247–249]. Overall, P-CABs were non-inferior to PPIs in healing EE and maintaining healed EE[250]. Interestingly, P-CABs were not superior to placebo in a phase III study in patients with NERD[251].

Prokinetics, such as metoclopramide, domperidone, mosapride, itopride and prucalopride, can enhance oesophageal peristalsis, increase LES basal pressure and accelerate gastric emptying. Prokinetics are usually given in addition to an anti-secretory drug, commonly a PPI. However, a meta-analysis revealed that the addition of a prokinetic to a PPI was associated with modest increases in symptom improvement, no improvement in healing or oesophageal motor activity, and increases in adverse events[252]. Consequently, prokinetics likely have more therapeutic value in patients with GERD and oesophageal or gastric hypomotility[253]. An important limitation to the use of prokinetics is their adverse effect profile,

Tachyphylaxis
Diminishing biological response to a given drug when it is administered continually.

especially drowsiness, tiredness, and tardive dyskinesia with metoclopramide and gynaecomastia, breast pain, and cardiac arrhythmias with domperidone. Baclofen, a γ-aminobutyric acid (GABA) B agonist, reduces TLESR rate and consequently reflux episodes, increases LES basal pressure and accelerates gastric emptying[254]. Baclofen is commonly administered as an add on to PPI once daily. Mucosal protectants, such as rebamipide, which promote the physiological protective barrier of the oesophageal mucosa, are also available in some regions or are in development[255,256].

Endoscopic procedures. Endoscopic procedures are positioned as an alternative for anti-reflux surgery and for chronic PPI treatment. Candidates for endoscopic therapy for GERD include patients with typical GERD symptoms (heartburn and regurgitation), low-grade EE (grade A or B), NERD, hiatal hernia <3 cm in size, and complete or partial response to PPI treatment[257]. Currently, three main endoscopic procedures for the treatment of GERD are in use[258]. The Stretta procedure delivers low-power, temperature-controlled radiofrequency energy into the area of the oesophagogastric junction, resulting in improvement in health-related quality of life, symptom score, the need for a PPI and oesophageal acid exposure[259]. The transoral incisionless fundoplication procedure creates an anterior full-thickness fundoplication, constructing a 3–5 cm anatomic valve that is 200–300° in circumference[260]. Similar to transoral incisionless fundoplication, the Medigus Ultrasonic Surgical Endostapler procedure creates a transoral incisionless anterior fundoplication of 270° using an ultrasound probe and a surgical stapler, which are located at the tip of the endoscope[261]. Both procedures were shown to provide similar effects to the stretta procedure on subjective and objective clinical endpoints. Limitations of these procedures include unknown durability, lack of normalization of oesophageal acid exposure in many patients, limited effect on oesophageal healing and no improvement in LES basal pressure[262–265]. Endoscopic treatment of GERD should only be conducted by experienced endoscopists who perform these procedures on a regular basis with a surgical backup[257]. Common complications include dysphagia, chest pain, sore throat, bloating and, less commonly, bleeding, perforation and mucosal tear[257]. Several meta-analyses published in the past few years raised concerns about the clinical value of these procedures, primarily because of the limited effect on objective clinical endpoints[262,263,266].

Surgery. Anti-reflux surgery is a therapeutic option for patients with GERD who consider medical therapy as unsatisfactory or undesirable. Anti-reflux surgery can reduce all types of reflux, including weakly acidic and weakly alkaline. The number of anti-reflux surgeries performed in the USA has considerably declined in the past decade owing to concerns about short-term and long-term complications, limited durability and the need for reoperation in some patients[267]. In addition, patients who currently undergo anti-reflux surgery tend to be older with a longer hospital stay, more post-surgery complications and higher mortality than previously reported[268,269]. Patients who are candidates for anti-reflux surgery include those who develop adverse effects or allergic reaction to pharmacological therapy, are not interested in pharmacological therapy, have poor compliance or wish to undergo surgery[235,260]. Patients with large hiatal hernia, regurgitation as the predominant symptom, abnormal oesophageal pH, or the presence of EE despite maximum PPI dose and those with symptoms that correlate with gastro-oesophageal reflux despite maximum PPI dose are also candidates for surgery. Predictors for successful anti-reflux surgery include the presence of typical GERD-related symptoms, symptomatic response to PPI treatment, abnormal pH test in patients with normal endoscopy, presence of EE and a highly experienced surgeon who regularly performs a high volume of anti-reflux procedures[270]. The work-up before anti-reflux surgery should include an upper endoscopy, pH test in the absence of medical therapy in patients with normal endoscopy, oesophageal manometry and possibly a barium swallow test[271,272].

Three surgical options are currently in use: variations of fundoplication, magnetic sphincter augmentation device (LINX), and Roux-en-Y gastric bypass in patients with morbid obesity and GERD[235]. Complete or partial surgical fundoplication creates a mechanical valve at the oesophagogastric junction by wrapping the gastric fundus around the lower part of the oesophagus and by reduction and repair of a hiatal hernia if present. The surgery prevents gastro-oesophageal reflux by restoration of the intra-abdominal portion of the oesophagus and, consequently, the angle of His and the LES flap valve, improvement of the sphincteric function of the crural diaphragm, bolstering the LES basal pressure, and reduction in the rate of TLESRs[273]. The clinical outcome of laparoscopic fundoplication is equivalent to open fundoplication, although the former is associated with less perioperative morbidity and the conversion rate to an open procedure is <5%[274]. Overall, partial fundoplication has similar outcomes to total fundoplication; however, partial fundoplication has a lower rate of dysphagia and an increasing number of surgeons prefer to perform this type of surgery[275]. Of the partial fundoplications, the laparoscopic posterior approach provides better results than the laparoscopic anterior approach[276,277]. Clinical outcomes of surgical fundoplication in patients with EE and in those with NERD do not differ[278,279]. Surgical fundoplication is at least as effective as continued medical therapy and, in some studies, was even superior to pharmacological therapy in controlling GERD symptoms[280–282]. Furthermore, surgical fundoplication is more effective in controlling oesophageal acid exposure and in improving GERD health-related quality of life measures than pharmacological therapy[282]. Anti-reflux surgery was also found to be more effective than adding medical therapy (a neuromodulator or baclofen) to PPI twice daily in patients with GERD with true PPI-refractory reflux-related heartburn[283]. In patients with refractory heartburn without a history of documented GERD, excluding functional heartburn should be a priority before anti-reflux surgery is considered. The adverse effects of surgical fundoplication include gas bloat syndrome, dysphagia, diarrhoea, reoperation

in up to 15% of patients and symptom recurrence in up to 62% of patients 11–13 years post-surgery[284].

The LINX is a miniature ring of interlinked titanium beads with a magnetic core that is placed around the oesophagogastric junction using a standardized laparoscopic procedure[285]. The ring augments sphincter competence and the surgery does not alter the anatomy of the oesophagogastric junction in contrast to surgical fundoplication[286]. The LINX procedure has been shown to be effective in improving objective and subjective clinical outcomes in patients with GERD, as good as surgical fundoplication in controlling GERD symptoms and better than PPIs in improving regurgitation[287–290]. The most common postoperative adverse effect is dysphagia[288]. However, studies assessing the long-term efficacy and safety of the LINX procedure are still needed.

Gastric bypass can be considered in patients with morbid obesity and GERD as an initial surgical approach or as a therapeutic option for those in whom surgical fundoplication was not successful[291,292]. This surgery is associated with less morbidity than surgical fundoplication in this group of patients and can decrease oesophageal acid exposure, reduce weight and improve obesity-related comorbidities[293].

Paediatric population

Treatment in children varies with age. In infants who have a high rate of non-acid reflux, conservative therapies, such as positioning and thickening of formula or milk, are first-line approaches. In older children in whom symptoms may be acid related, acid suppression is the first-line therapy.

Positioning. The evidence for a reduction of reflux events with upright positioning is not conclusive[294,295]. However, in pH–impedance studies, infants have the lowest number of reflux episodes in the prone position followed by the left lateral decubitus position, and then the right lateral decubitus position and supine position. Importantly, the American Academy of Paediatrics and North American Society For Paediatric Gastroenterology, Hepatology & Nutrition (NASPGHAN) guidelines recommend that, despite possible reflux benefits to alternative positions, the increased risk of sudden infant death syndrome in any position other than supine outweighs the risk of gastro-oesophageal reflux.

Thickening and cow milk protein restriction. Thickening of infant formula or breast milk is a mainstay of treatment for infant reflux. It reduces aspiration risk in infants with oropharyngeal dysphagia and also reduces visible regurgitation and vomiting, which may have benefits to children with impaired airway protective mechanisms. Studies have shown that thickening reduces the number of vomiting or visible regurgitation episodes but the total number of reflux episodes, measured by pH–impedance, is not decreased[296,297]. Thickening has been used in gastrostomy-fed children to reduce symptoms of gastro-oesophageal reflux and reflux-associated hospitalizations in children with medical complexity[298].

Because of the complete overlap of symptoms of GERD and cow milk protein allergy or intolerance in infants, current therapeutic algorithms for GERD in infants include a 2-week trial of a protein hydrolysate formula or an amino acid-based formula to assess for symptom resolution[299].

Acid suppression. PPIs heal oesophagitis in ≥80% of children >6 months of age after 8 weeks of therapy and are the gold standard for the treatment of erosive and microscopic acid-related oesophagitis in these patients[300–302]. However, their efficacy in symptom improvement varies by age and by symptom type. Multiple studies in infants, including placebo-controlled randomized trials, did not show a benefit of PPIs in reducing symptoms of crying, arching, cough, fussiness and hoarseness[303,304]. Nevertheless, up to 70% of infants are prescribed PPIs for symptoms of regurgitation, fussiness and feeding difficulty[305–307]. Based on this evidence, PPIs are not routinely recommended for symptom control in infants and, if used, they should only be used for short trials and only continued if there is clear, objective evidence of symptomatic improvement[59]. In older children with typical symptoms, such as abdominal and epigastric pain, heartburn and chest pain, open-label and uncontrolled trials of PPI indicate possible symptomatic improvement[300,308,309].

For the treatment of extra-oesophageal symptoms, a single study using lansoprazole found no benefit in improving respiratory outcomes, including steroid use and emergency room visits, even in the subgroup of patients with abnormal pH-metry[310]. Consequently, PPIs are not recommended for extra-oesophageal symptoms unless there is clear evidence of acid-related typical symptoms[59].

Similar to PPIs, there is clear evidence of mucosal healing in >60% of patients taking 8 weeks of H2RAs such as ranitidine and famotidine[311,312]. Only one study showed some benefit of H2RAs in improving symptoms of regurgitation in infants and children but crying, distress, heartburn or colic did not improve[312]. H2RAs are currently used as a second-line therapy for oesophagitis, when less aggressive acid suppression than with PPIs is needed or PPIs have adverse effects.

Adverse events of acid suppression have been reported for both H2RAs and PPIs in case-controlled paediatric studies and randomized trials with the primary risk resulting from disturbances of the microbiome with resultant infection risk[313–315]. Children treated with acid suppression have increased risks of upper respiratory tract infections, pharyngitis, pneumonia, sepsis, acute gastroenteritis, *Clostridium difficile* infection and necrotizing enterocolitis[314,316–318]. Several studies suggest an increased risk of allergies in infants of mothers who took PPIs during pregnancy and in infants exposed to acid suppression medications[319,320]. In one study, PPI use was associated with an increased risk of fracture and this risk was greater for higher doses of acid suppression and earlier age of onset of PPI use[321].

Prokinetics. There is no evidence that metoclopramide or erythromycin treat symptoms of gastro-oesophageal reflux in infants or children and no other prokinetics are approved in this patient group[59]. In one randomized

placebo-controlled trial of erythromycin to treat gastro-oesophageal reflux in infants in an ICU setting, reflux parameters measured by pH-metry did not improve, although feeding tolerance may improve possibly owing to a motility benefit[322,323]. Prucalopride, a 5HT4 receptor agonist, has been used in children with medical complexity at risk of considerable complications from gastro-oesophageal reflux disease[324–326].

Fundoplication. The main indication for fundoplication in children is reflux that results in cardiopulmonary compromise or to treat those who have complications from medical therapy[59]. Similar to studies in adults, paediatric patients who respond to acid suppression therapy or transpyloric feeding are more likely to respond to fundoplication therapy. However, database studies have not shown improvements in pulmonary outcomes, such as mechanical ventilation, hospitalizations or pneumonia frequency, after fundoplication[327–330]. Transpyloric feeding is frequently used as an alternative to fundoplication in children and outcomes and reflux burden are equivalent for fundoplication and transpyloric feeding[331,332].

Quality of life

GERD has substantial adverse effects on the health-related quality of life (HRQoL) of patients. Based on generic HRQoL questionnaires, such as the Short Form Health Survey or SF-36, the reduction in their HRQoL equals or is even larger than that of patients with diseases such as diabetes mellitus, arterial hypertension, myocardial infarction, arthritis or congestive heart failure[333–337]. In a German study that evaluated >6,000 patients with GERD consulting general practices, pain and poor health, physical and emotional well-being and functioning were substantially impaired compared with the general population, irrespective of the presence of oesophagitis[338]. This finding indicates that symptoms rather than mucosal inflammation dictate the reduction in quality of life (QoL).

To better appreciate the effect of GERD symptoms on HRQoL, disease-specific QoL questionnaires, such as the QOLRAD (Quality of Life in Reflux and Dyspepsia) or Reflux-Qual (Quality of Life Questionnaire in Gastroesophageal Reflux) have been developed, assessing emotional distress, problems with drinking and eating, sleep disturbances, physical and social functioning, vitality, and others. These instruments confirm a reduction in HRQoL in patients with GERD[339,340] and reveal that improvement of symptoms during PPI treatment is associated with a considerable increase in HRQoL. By contrast, HRQoL remains reduced in those whose symptoms persist during treatment[338,339]. Similarly, control of GERD symptoms through laparoscopic fundoplication in adults and children has a positive effect on HRQoL, further underscoring the importance of adequate treatment[341,342].

Patients with more frequent and severe reflux symptoms or with persistent symptoms during PPI treatment have lower HRQoL scores than those with less frequent or severe symptoms or those who respond to PPI treatment[339,340]. The threshold to consider heartburn or regurgitation as clinically relevant, that is, having a substantial effect on HRQoL, has been defined as >2 days per week of mild heartburn or >1 day per week of at least moderate heartburn[1] and >4 days per week for regurgitation[343]. The reduction in HRQoL in GERD owing to regurgitation is incremental to that associated with heartburn[343]. Notably, regurgitation is more resistant to PPI treatment than heartburn and therefore seems to play a major role in the apparent failure of PPI treatment in GERD and the reduced HRQoL in PPI partial responders. Of note, reflux symptoms substantially affect all health-related items assessed. Not only decreased physical and mental health but also sleep disturbances contribute to the reduced HRQoL in GERD[340,344]. Greater overall symptom severity and nocturnal symptoms are major factors that decrease sleep quality[345]. Most likely, sleep disturbance is one of the main reasons for the considerable increase in absenteeism and presenteeism (reduced productivity while at work) reported in GERD[345–348]. Together with increased health-care utilization, all these factors lead to a substantial burden on the economic and health-care system, further emphasizing the need for the more efficient management of patients with GERD.

Outlook

Further research is particularly required in the areas of GERD pathophysiology, diagnosis and management. For GERD pathophysiology, understanding the composition and location of a postprandial gastric acid pocket will enable to improve the management of GERD. Long-term non-invasive quantification of reflux volume (distension) and composition (gas, acid, bile acids and enzymes) will help to understand differences between GERD phenotypes and enable personalized treatment. The detection of impairment of oesophageal mucosal integrity enables the assessment of progression or regression from one GERD phenotype to another. In addition, identifying the presence of oesophageal hypersensitivity will help to better tailor treatment, particularly in patients with NERD. The role of microinflammation, mucosal integrity impairment and mucosal innervation (position of nerves and presence of different molecular receptors) is under investigation and may lead to oesophageal mucosal topical protective strategies.

For GERD diagnosis, improving testing is important to correctly identify the disease and provide appropriate care. Alternative strategies should be explored to measure the long-term effect of GERD on oesophageal epithelium, specifically, how these oesophageal changes can be used by mucosal integrity testing, on or off therapy, to diagnose the presence or absence of GERD. In addition, delineating the roles of pharmacological, endoscopic or surgical approaches in treating patients with confirmed GERD will improve our care of this important group.

For GERD treatment, the disease remains an attractive area for drug development, primarily because of its high prevalence and symptom burden and the many areas of unmet need despite the availability of several PPIs. P-CABs are already available in some regions and more are in development; the effect of their introduction into the European and US markets, especially on the prescribing patterns of PPIs, remain to be seen. P-CABs are

likely to have the most important effect on the therapeutic landscape of GERD in the coming decade. Another area of possible future development are mucosal protectants that aim to prevent oesophageal mucosal injury or restore normal oesophageal mucosal integrity. The potential value of neuromodulators in treating oesophageal hypersensitivity will be the focus of investigation in patients with NERD. The use of behavioural approaches, nutritional interventions, alternative and complementary medicine will continue to expand, particularly in patients with refractory GERD and FEDs. Simpler new endoscopic techniques with better safety profiles and improved efficacy are being explored. Finally, therapeutic strategies for emerging GERD populations will be developed such as those with GERD after bariatric surgery.

In the paediatric population, the past decade has seen a shift in the diagnosis and treatment of gastro-oesophageal reflux towards the measurement and treatment of non-acid reflux. pH–impedance studies have consistently shown high rates of non-acid reflux, explaining the lack of efficacy of acid suppression in infants and toddlers. Future paediatric research should focus on new treatments of non-acid reflux, including motility interventions that improve gastric emptying and oesophageal clearance of refluxate.

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Author contributions

Introduction (R.F.); Epidemiology (H.E.-S. and R.R.); Mechanisms/pathophysiology (D.S. and R.R.); Diagnosis, screening and prevention (M.F.V. and R.R.); Management (R.F. and R.R.); Quality of life (G.E.B.); Outlook (R.F., D.S., M.F.V. and R.R.); Overview of the Primer (R.F.).

Competing interests

R.F. receives adviser/speaker/consultant honoraria from Takeda, Daewoong, Medtronic, Phathom Pharmaceuticals, Neurogastrx, GERDCare, AstraZeneca, Eisai Pharmaceuticals and Johnson & Johnson. M.F.V. receives adviser/speaker/consultant honoraria from Ironwood, Phathom Pharmaceuticals and Diversatek; research funding for M.F.V. is provided by Diversatek. Research funding for D.S. is provided by Reckitt Benckiser, Jinshan Technology and Alfa Sigma. R.R., H.E.-S. and G.E.B. declare no competing interests.

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