nature reviews gastroenterology & hepatology

https://doi.org/10.1038/s41575-023-00883-z

Review article

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Pathophysiology of gastro-oesophageal reflux disease: implications for diagnosis and management

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Abstract

Gastro-oesophageal reflux disease (GERD) is a common gastrointestinal disorder in which retrograde flow of gastric content into the oesophagus causes uncomfortable symptoms and/or complications. It has a multifactorial and partially understood pathophysiology. GERD starts in the stomach, where the refluxate material is produced. Following the trajectory of reflux, the failure of the antireflux barrier, primarily the lower oesophageal sphincter and the crural diaphragm, enables the refluxate to reach the oesophageal lumen, triggering oesophageal or extra-oesophageal symptoms. Reflux clearance mechanisms such as primary and secondary peristalsis and the arrival of bicarbonate-rich saliva are critical to prevent mucosal damage. Alterations of the oesophageal mucosal integrity, such as macroscopic oesophagitis or microscopic changes, determine the perception of symptoms. The intensity of the symptoms is affected by peripheral and central neural and psychological mechanisms. In this Review, we describe an updated understanding of the complex and multifactorial pathophysiology of GERD. It is now recognized that different GERD phenotypes have different degrees of reflux, severity of mucosal integrity damage and type, and severity of symptoms. These variations are probably due to the occurrence of a predominant pathophysiological mechanism in each patient. We also describe the main pathophysiological mechanisms of GERD and their implications for personalized diagnosis and management.

Sections

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Key points

- Gastro-oesophageal reflux disease (GERD) is a common gastrointestinal disorder and has a multifactorial pathophysiology; there are two phenotypes of GERD, erosive and non-erosive reflux disease, and their distinct pathophysiology is not completely known.
- The oesophagogastric junction works as a functional antireflux barrier; transient lower oesophageal sphincter relaxations are the most frequent mechanism for reflux in healthy individuals and in patients with GERD. Hiatal hernia is an important mechanism of GERD.
- Motility impairment of both the oesophagus and the proximal stomach is involved in GERD pathophysiology.
- The refluxate is a mix of gastric and biliopancreatic secretions. Acid reflux is associated with heartburn and mucosal damage. Bile reflux provokes more severe oesophagitis or Barrett oesophagus. Non-acid reflux is mainly associated with symptoms but no mucosal damage.
- Impairment of oesophageal mucosal integrity, innervation and microinflammation has a crucial role in symptom perception.
- Severity of GERD symptoms is influenced by psychoneuroimmune modulation; psychosocial comorbidities and hypervigilance determine the severity of GERD symptoms as well as response to treatment.

Introduction

Gastro-oesophageal reflux disease (GERD) is a common gastrointestinal disorder, with a variable global prevalence of 18.1–27.8% in North America, 8.8–25.9% in Europe, 2.5–7.8% in East Asia, 8.7–33.1% in the Middle East, 11.6% in Australia and 23.0% in South America[1,2]. It is a condition in which retrograde flow of gastric content into the oesophagus causes uncomfortable symptoms and/or complications[3].

GERD has a multifactorial and partially understood pathophysiology. The process starts in the stomach, where gastric secretions together with biliopancreatic components constitute the refluxate material. In GERD, a failure of the antireflux barrier, which mainly consists of the lower oesophageal sphincter (LES) and the crural diaphragm, is critical. When the refluxate reaches the oesophageal lumen, its contact with the oesophageal mucosa can trigger reflux symptoms, either oesophageal or extra-oesophageal. The degree and duration of such contact will depend on clearance mechanisms such as primary or secondary peristalsis and the arrival of swallowed neutralizing saliva.

The breakdown of protective mucosal mechanisms can compromise mucosal integrity, potentially leading to visible oesophagitis or subtle inflammation. These conditions have a pivotal role in symptom perception and may contribute to additional mucosal harm. The intensity and characteristics of symptoms are modulated by a combination of peripheral and central neural and psychological control mechanisms[4].

In this Review, we describe the multiple pathophysiological factors involved in GERD by following the trajectory of reflux. First, we discuss gastric factors, followed by anatomical and functional failures of the gastro-oesophageal antireflux barrier. Then, we discuss the different types of refluxate and the effect of such refluxate on the oesophageal mucosa. Next, we analyse the mechanisms of clearance after reflux has occurred. Last, we discuss the mechanisms of symptoms perception, both at the mucosal level and in terms of psychological and neural central modulation (Fig. 1). At the end of each section, we suggest diagnostic and treatment implications for each of the pathophysiological mechanisms described (Table 1).

Gastric and biliopancreatic factors

The composition and distribution of gastric contents change depending on ingested meals, gastric and biliopancreatic secretion, and gastroduodenal motility. After a meal, the gastric contents is mainly located in the proximal stomach and is gradually emptied into the distal stomach and the duodenum.

Composition and distribution of gastric contents

Postprandial acid and bile pockets. Acid reflux, and its associated symptoms, occurs most frequently after meals[5]. In healthy individuals and patients with GERD, Fletcher and colleagues have shown that there is an area of acidic gastric content, at and just below the oesophagogastric junction (EGJ), that escapes the buffering effect of meals: a postprandial 'acid pocket'[6]. A bile pocket has also been described in the same area in patients with GERD[7,8].

This acid pocket can extend across the sphincter into the distal oesophageal body and can be the source of short-segment acid reflux episodes (detected up to 2–3 cm above the proximal margin of the LES)[9,10]. It has been proposed that chronic short-segment reflux episodes might lead to mucosal inflammation and metaplasia at the EGJ and distal oesophagus[11]. The acid pocket is a physiologically normal phenomenon; however, patients with GERD have larger acid pockets than healthy individuals[11].

***Helicobacter pylori*, gastric acid secretion and GERD.** Inflammation of the gastric corpus mucosa secondary to *H. pylori* infection can have a protective effect against GERD because of the reduction of acid secretion owing to gastric mucosal atrophy[12]. However, antrum-predominant gastritis induces hypergastrinaemia and increased intragastric acidity; consequently, the risk of GERD increases in patients with antral gastritis[12]. Abe and colleagues reported a prevalence of *H. pylori* of 71% in patients without GERD symptoms compared with 30%, 16% and 0% in patients with oesophagitis, short-segment Barrett oesophagus and long-segment Barrett oesophagus, respectively[13]. El Serag and colleagues have shown that *H. pylori* gastritis was associated with a 54% (95% CI 21–73) reduced risk of oesophagitis[14]. Regional differences in the prevalence and virulence of *H. pylori* strains can have an effect on the relationship between *H. pylori* and GERD. *H. pylori* strains that are cagA positive are more commonly associated with corpus gastritis and, in consequence, with a lower prevalence of oesophageal GERD complications[15].

Gastric motility

Gastric accommodation and gastric emptying. Food ingestion induces a reflex relaxation of the proximal stomach, which is called accommodation, followed by a gradual tonic contraction to deliver food into the more distal gastric antrum[16]. An abnormal accommodation reflex can increase reflux volume[16]. Gastric motor abnormalities in GERD include enhanced and prolonged postprandial fundus relaxation or delayed recovery of postprandial proximal stomach tone[17,18]. Delayed gastric emptying has been described in up to 40% of patients with GERD[19]. However, there is a poor correlation between duration of gastric emptying and oesophageal acid exposure[20]. Emerenziani

and colleagues compared the proximal extent of gastro-oesophageal reflux during fasting and postprandial conditions in patients with GERD and healthy individuals. They found that reflux episodes are more likely to reach the proximal oesophagus during the early postprandial period, suggesting that delayed gastric emptying might have an effect on the proximal extent of reflux rather than total acid exposure[21].

GERD and functional dyspepsia symptoms frequently overlap. Gonlachanvit and colleagues studied gastric emptying in patients with GERD and functional dyspepsia[22]. They showed that gastric contents in the proximal stomach was significantly greater in patients with GERD and functional dyspepsia than in healthy individuals. Regarding symptoms, patients with acid regurgitation, vomiting, early satiety and abdominal distention have larger proximal gastric retention than healthy individuals. By contrast, distal gastric retention was smaller in patients with heartburn and acid regurgitation and greater in patients with postprandial nausea. Proximal gastric retention was observed in patients with GERD, and distal gastric retention was predominant in patients with functional dyspepsia[22].

Effect of obesity on gastric physiology and reflux. Obesity has an important role in the pathophysiology of GERD. For every unit increase of body mass index (BMI), the time of distal oesophageal pH < 4 increased by 0.35% (95% CI 0.24–0.46)[23]. Patients with obesity frequently develop hiatal hernia associated with a low LES pressure[24]. In individuals with obesity, large, high-calorie meals are associated with delayed gastric emptying, fundic distention and more transient LES relaxations (TLESRs) causing reflux[24]. Obesity-related hormonal changes can also predispose individuals to reflux complications, such as oesophageal cancer[25]. The odds ratio (OR) estimated for GERD is 1.8 for people with overweight and 2.6 for people with obesity[26,27]. As BMI increases, the prevalence of GERD symptoms (OR 2.44; 95% CI 1.27–4.67) and oesophagitis (OR 2.75; 95% CI 1.24–6.13) also increases[28].

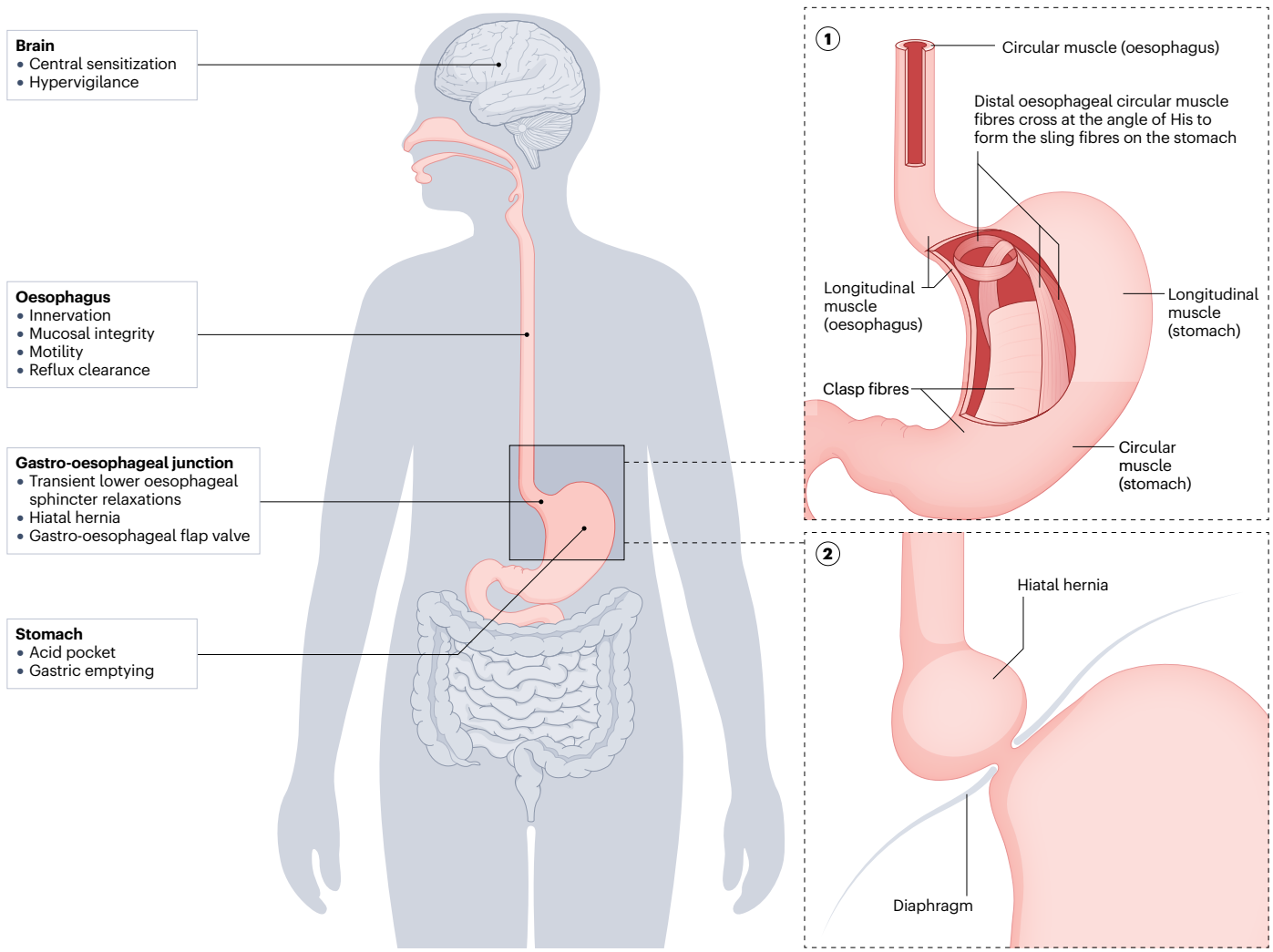

Fig. 1 | Multifactorial pathophysiology of GERD. The path of reflux and the most relevant elements involved at each stage in the pathophysiology of gastro-oesophageal reflux disease (GERD). (1) Normal gastro-oesophageal junction. The lower oesophageal sphincter and the crural diaphragm form a complex structure integrated by circular, longitudinal and clasp fibres that work together as a functional unit to prevent reflux. (2) Hiatal hernia. The most common anatomical alteration that predisposes to GERD. Adapted with permission from ref. 84, Acta Gastroenterológica Latinoamericana.

Table 1 | Pathophysiological mechanisms of GERD and their management implications

Pathophysiological mechanism		Management implications
Gastric and biliopancreatic factors		
Composition and distribution of gastric contents	Postprandial acid and bile pockets[6]	Capping the acid pocket with alginates can reduce acid and bile reflux
	Helicobacter pylori, gastric acid secretion and GERD[12]	*Helicobacter pylori* is associated with a lower prevalence of reflux; however, it should be eradicated because it is strongly linked to gastric adenocarcinoma
Gastric motility	Gastric accommodation and gastric emptying[17,18]	Delayed gastric emptying should be managed with diet modification and prokinetics; these patients might have increased postprandial reflux with proximal extent and risk of extra-oesophageal reflux
	Bariatric surgical procedures and GERD[30]	Patients with GERD and obesity should focus on weight loss by either diet or bariatric surgery
Gastro-oesophageal antireflux barrier		
Anatomical and functional composition of the oesophagogastric junction	Decreased LES pressure[56]	Prokinetics such as prucalopride can be used if LES pressure is very low
	TLESRs[56]	In postprandial belch-related reflux associated with TLESRs, baclofen can reduce the rate of TLESRs; treatment of prandial aerophagia with diet changes and sitting in an upright position during meals is an alternative
	Swallow-associated LES relaxations[45]	Most frequent in patients with hiatal hernia
	Hiatal hernia[54]	Diagnosis can occur during endoscopy, barium swallow or high-resolution manometry, which provides the most precise diagnosis When a hiatal hernia is considered the main pathophysiological mechanism of reflux in a patient with reflux symptoms and pathological reflux monitoring, surgical treatment seems to be the best alternative, particularly when the hiatal hernia is larger than 3 cm
Refluxate		
Chemical and gas/liquid composition of the refluxate	Acid reflux[78,81]	PPIs should be adjusted to the reflux pattern, that is, twice daily in the presence of supine acid reflux; new potassium-competitive acid blocker medication to reduce acid secretion can be considered Owing to the day-to-day variability in oesophageal acid exposure and symptoms, prolonged wireless pH monitoring can identify patients with difficult diagnosis of GERD and provide a guideline for PPI management[78]
	Bile reflux[82]	Bile reflux has a major role in the pathogenesis of severe GERD; new bile acid sequestrants are under investigation
	Gas reflux[70,71]	A significant proportion of patients with GERD have reflux related to belching; in some patients, this is secondary to aerophagia during meals followed by postprandial gastric belching; and in other patients, reflux is related to supragastric belching Many of these patients are refractory to PPI treatment: for aerophagia and gastric belching, dietary habits and baclofen can be used; for supragastric belching, cognitive behavioural therapy is recommended
Oesophageal clearance after reflux		
Oesophageal peristalsis and volume clearance[85,87]		Evaluation of oesophageal motility in patients with reflux symptoms is useful to identify severe oesophageal hypomotility Currently, there is not a safe and efficient prokinetic for oesophageal hypomotility When an oesophageal hypomotility disorder is diagnosed, assessing muscle reserve through the multiple rapid swallow test is clinically relevant; the absence of adequate peristaltic wave after the multiple rapid swallow test is more often associated with post-surgical dysphagia To record all the medications that the patients consume, especially in the older population; anticholinergics, antidepressant and opioids can significantly affect oesophageal motility Surgical or endoscopic treatment strategy, based on status of oesophageal motility, remains controversial
Swallowed saliva and chemical clearance[88,89]		After refluxed stomach contents are cleared by peristalsis, the lower oesophageal mucosa remains acidic; saliva, containing bicarbonate, helps to neutralize acid and promote mucosal healing Reduced salivation owing to ageing, medications and conditions such as chronic dry mouth can lead to prolonged acid clearance times, particularly during sleep We suggest enquiring about symptoms of xerostomia, especially in the elderly population
PSPW[90]		An abnormal PSPW index during pH-impedance monitoring can be useful for diagnosis of GERD in patients with inconclusive diagnosis
Oesophageal mucosa		
NERD 85		NERD is diagnosed when there is pathological acid exposure and a normal endoscopy performed 'off' PPIs
ERD[106]		Mild oesophagitis (LA Classification grades A and B) should be managed with standard PPI dosing and does not require further endoscopic controls Severe oesophagitis (LA Classification grades C and D) requires PPIs bid for 8 weeks and further endoscopic control

Table 1 (continued) | Pathophysiological mechanisms of GERD and their management implications

Pathophysiological mechanism	Management implications
Oesophageal mucosa (continued)	
Barrett oesophagus[107]	Barrett oesophagus should be managed with standard PPI dosing to treat reflux symptoms and heal oesophagitis and escalation of dosing for patients with inadequate symptom control Regarding dysplasia, all guidelines recommend endoscopic ablative therapy for high-grade dysplasia and most guidelines extend this recommendation to low-grade dysplasia
Oesophageal symptoms perception	
Central and peripheral neural modulation[120]	In patients with oesophageal hypersensitivity, there is a central abnormal modulation and a peripheral mucosal neuroimmune alteration In oesophageal hypersensitivity, the pain modulators and a topical mucosal protection can reduce the symptoms
Hypervigilance[123–125]	Hypervigilance in patients with oesophageal symptoms and psychological management of hypervigilance are useful

ERD, erosive reflux disease; GERD, gastro-oesophageal reflux disease; LES, lower oesophageal sphincter; NERD, non-erosive reflux disease; PPI, proton pump inhibitor; PSPW, post-swallow-induced peristaltic wave; TLESR, transient lower oesophageal relaxation.

Bariatric surgical procedures. Today, there are several surgical therapies for severe obesity, such as Roux-en-Y gastric bypass, sleeve gastrectomy, adjustable gastric banding and biliopancreatic diversion with duodenal switch[29]. Although the main treatment for severe GERD continues to be fundoplication (EGJ repair and creation of a gastric fundus wrap around the EGJ), bariatric surgery is an alternative treatment for patients with obesity and GERD[30].

Sleeve gastrectomy is the most frequently restrictive procedure (to decrease gastric volume)[31]. It is associated with an increased prevalence of GERD symptoms and oesophagitis. Moreover, the prevalence of Barrett oesophagus seems to increase in patients after sleeve gastrectomy[24,31]. Gastric bypass with Roux-en-Y diversion is the most complex and best-investigated bariatric intervention. The anatomical changes after this surgery are associated with fewer reflux events than sleeve gastrectomy[32].

Gastrectomy. Vaezi and Richter characterized patients with gastro-oesophageal reflux after partial and total gastrectomy. These patients can have reflux with a combination of acid, bile and other pancreatic enzymes[8]. In patients who have undergone a total gastrectomy, gastric acid is eliminated and only duodeno-oesophageal reflux occurs. This type of reflux contains bile acids and pancreatic enzymes that can provoke oesophageal mucosal damage and symptoms[8,33]. They found that acid production might not be completely eliminated in some patients who underwent partial gastrectomy[33]. Oesophageal mucosal injury occurred mostly in the subgroup of patients who had mixed refluxate (duodenal content and gastric acid). Reflux of acid and duodenal content produces heartburn, abdominal pain and regurgitation, whereas nausea, vomiting and distension were predominant symptoms in patients with non-acidic duodeno-gastric-oesophageal reflux[33].

Gastric pepsin. Pepsin is an enzyme produced in the stomach that helps to break down proteins into smaller peptides during the process of digestion. There are two mechanisms by which pepsin can be activated. The first is by exposure to acid; in fact, alkaline pH inactivates pepsin[34]. The second mechanism is by intracellular activation after epithelial cell uptake. Pepsin can cause direct cell damage through the destruction of extracellular proteins and intercellular junctions, and indirect cell damage owing to disruption of cellular defences[35]. In addition to its role in the pathophysiology of mucosal damage, measurement of salivary pepsin has been proposed as a non-invasive method for GERD diagnosis. However, variable and non-reproducible results have been published so far, preventing the clinical use of salivary pepsin for diagnosis of GERD[34,36].

Implications for diagnosis and management

In patients with overlapping symptoms of GERD and dyspepsia, measurement of gastric emptying time can demonstrate substantial delayed gastric emptying. In these patients, diet modification and prokinetic agents are recommended. Patients with delayed gastric emptying might have increased postprandial reflux, with high proximal extent and risk of extra-oesophageal reflux[21]. They should avoid supine positions and physical exercises after meals. Capping the acid pocket with alginates or modifying the acid distribution within the stomach with prokinetic agents such as azithromycin can reduce acid and bile reflux, particularly in patients with hiatal hernia[37].

Although *H. pylori* is associated with a lower prevalence of reflux, it should be eradicated because it is strongly linked to gastric adenocarcinoma. Patients with GERD and obesity should focus on weight loss, by either diet or bariatric surgery.

Gastro-oesophageal antireflux barrier

Anatomical and functional composition of the EGJ

The EGJ is a complex anatomical structure that works as a functional unit by acting as an antireflux barrier. It is mainly composed of the LES, the crural diaphragm and the 'flap valve', formed by the phrenoesophageal ligament and annular fibres of the gastric cardia[38] (Fig. 1).

Four main mechanisms are considered a failure of the antireflux barrier: decreased LES basal pressure, TLESRs, swallow-associated LES relaxations and hiatal hernia.

Decreased LES pressure. The normal basal LES pressure in adults is 10–30 mmHg. It is higher in the supine position and decreases during postprandial periods[39]. It can be affected by intra-abdominal pressure, gastric distention, peptides, hormones, foods and medications[40].

Although patients with GERD can have a lower mean basal LES, most of them have normal-range basal LES pressure. A subgroup of patients with GERD and oesophagitis has manometric LES pressures lower than 10 mmHg (ref. 39).

TLESRs. TLESRs are spontaneous LES relaxations that are not induced by swallowing. They are the most frequent mechanism of reflux in

healthy individuals and in patients with GERD[41,42]. They are triggered by a mechanosensitive reflex mechanism initiated by gastric distension that induces the activation of inhibitory neurons that release nitric oxide to relax the LES[41,42]. TLESRs are also associated with inhibition of the crural diaphragmatic contraction and shortening of the oesophageal body owing to the contraction of its longitudinal muscle layer[41,42]. Unlike swallow-induced LES relaxations, which last 5–7 seconds, TLESRs last longer (>10 seconds)[43]. Most TLESRs occur within 2 hours after a meal[44]. This is a physiological phenomenon that occurs in healthy individuals as frequently as in patients with GERD.

However, compared with TLESRs in healthy individuals, they are more often associated with acid reflux in patients with GERD[43].

Swallow-associated LES relaxations. Studies using prolonged ambulatory oesophageal manometric monitoring have shown that most reflux episodes in healthy individuals and in patients with mild oesophagitis occur during TLESRs[41]. However, in patients with moderate or severe oesophagitis and in patients with hiatal hernia, a greater proportion of reflux episodes occurs during swallow-associated LES relaxations rather than during TLERSs[45].

Hiatal hernia. A hiatal hernia is an anatomical defect at the EGJ where a portion of the stomach protrudes into the chest cavity. Hiatal hernia promotes reflux of gastric material into the oesophagus[46] (Fig. 1). Under normal conditions, the LES and the crural diaphragm overlap at the same level and both contribute to the gastro-oesophageal barrier. During expiration, the pressure slightly increases in the oesophagus and mostly does not change in the stomach. Therefore, the gastro-oesophageal pressure gradient is low, and the LES pressure is high enough to avoid reflux. However, during inspiration, the intragastric pressure increases and the oesophageal pressure decreases. As a result, the pressure gradient is higher, and the LES pressure has to increase to avoid reflux. During deep inspiration, straining or coughing, the pressure gradient between the stomach and the oesophagus can rise to 100 mmHg or more. This normally does not result in reflux because of a strong contraction of the crural diaphragm, which increases the pressure of the EGJ up to 150 mmHg (ref. 47). When the LES and the diaphragmatic crura do not overlap, in the presence of a hiatal hernia, reflux is facilitated. The crural diaphragm suffers axial displacement and radial disruption, secondary to dilation or enlargement of the hiatal orifice[48]. Larger hernias (>2 cm) cause widening of the oesophageal hiatus, which can impair the ability of the crural diaphragm to function as a sphincter[49]. In the context of a hiatal hernia, the contraction of the diaphragmatic crura during inspiration generates a compartmentalization and increased pressure within the hernia between the LES and the diaphragm, which increases the likelihood of a reflux episode[46].

Hiatal hernia increases the risk of Barrett oesophagus and is most strongly associated with long-segment Barrett oesophagus[50]. In addition, obesity is associated with a higher risk of hiatal hernia[51]. This could be due to increased intra-abdominal pressure, which positively correlates with BMI[52]. Oesophageal body motor function and oesophageal clearance have been found to be disrupted in patients with hiatal hernia. This is more the case in patients with a fixed hernia (non-reducing) than in those with a sliding hiatal hernia.[52,53].

A recent study has shown that patients with hiatal hernia have lower oesophageal mucosal baseline impedance than those with similar total acid exposure but no hiatal hernia. It has been suggested that the more-severe impairment of mucosal integrity in hiatal hernia might be due to increased bile reflux in these patients[54].

Implications for diagnosis and management

Hiatal hernia can be diagnosed using endoscopy, a barium swallow test or high-resolution manometry (HRM). HRM provides the most precise diagnosis. During HRM, the distance between the LES and the diaphragmatic crura can be accurately measured without being affected by oesophageal and/or gastric distensions such as those provoked during endoscopy. When a hiatal hernia is considered to be the main pathophysiological mechanism of reflux in a patient with reflux symptoms and pathological reflux monitoring, surgical treatment seems to be the best alternative, particularly when the hiatal hernia is larger than 3 cm (ref. 55). Prokinetics such as prucalopride can be used in patients with reflux during very-low LES pressure. However, this treatment is not widely used. In patients with postprandial belch-related reflux that occurs during TLESRs, baclofen can be used to reduce the rate of TLESRs[56]. However, owing to secondary effects, this drug is not well tolerated by many patients. Finally, endoscopic procedures, such as transoral incisionless fundoplication, non-ablative radiofrequency treatment and others, should be reserved for EGJ incompetence with minor anatomical defects[56].

The refluxate

Composition

The critical components of refluxate are hydrochloric acid, pepsin, biliopancreatic enzymes, microbial pathogens and bicarbonate[57]. Reflux episodes can be pure liquid but more often they are a mixture of liquid and gas[58]. The presence of gas in the refluxate has been shown to increase the chance of reflux perception[58]. The refluxate can be acidic (pH < 4), weakly acidic (pH > 4) or non-acidic (pH > 6)[59].

Acid reflux. Acid reflux is associated with both symptoms (heartburn, regurgitation or chest pain) and mucosal damage, particularly when it also contains bile acids. Greater exposure of the oesophagus to acid correlates with severity of oesophageal mucosal damage[60]. Heartburn and regurgitation are more likely to occur when the drop in oesophageal pH is prolonged, the refluxate reaches the proximal oesophagus and oesophageal clearance is delayed[61].

Weakly acidic and non-acid reflux. In the early postprandial period, reflux episodes can be weakly acidic owing to the buffering effect of a meal[62]. Gastric juice remains weakly acidic (pH 4–6) in patients 'on' proton pump inhibitor (PPI) treatment[62]. Weakly acidic and non-acid reflux (without bile acids) do not cause oesophageal mucosal damage, but they have been implicated in oesophageal symptoms such as regurgitation or chest pain and extra-oesophageal symptoms such as cough[62]. Non-acid reflux is the main type of reflux in neonates[63].

Bile reflux. The exposure of the oesophageal mucosa to acidic bile reflux is associated with more-severe damage than non-acidic bile reflux[64,65]. Experimental evidence in the rabbit oesophagus has shown that contact between the oesophageal mucosa and weakly acid solutions containing bile acids increased mucosal permeability and intercellular space dilation[66]. Moreover, the positive correlation between bile acid concentration in the refluxate and severity of reflux symptoms might be explained by the observation that bile acids increase mucosal permeability to hydrogen ion absorption[67].

When it comes to erosive oesophagitis and Barrett oesophagus, an association between mucosal exposure to bile acids and presence of inflammatory cytokines has been identified. An increase in the expression of IL-6, IL-8, COX2 and TNF as well as an increase in the recruitment of inflammatory cells have been observed[68]. Dvorak and colleagues

have shown that bile acids can induce the release of reactive oxygen species in ex vivo Barrett oesophagus tissue, which can lead to DNA damage and increase the risk of metaplasia[69].

Gas reflux. The development of pH and impedance monitoring enabled assessment of intra-oesophageal gas movement. It is possible to distinguish the direction of gas movement, that is, anterograde (swallow) or retrograde (reflux). Gas reflux, also known as belching, has been categorized into supragastric belching and gastric belching[70]. In supragastric belching, air enters and leaves the oesophagus rapidly without reaching the stomach. Supragastric belching is commonly detected in patients with GERD symptoms[70] and, in some of these patients, supragastric belching is associated with increased acid reflux[71]. Gastric belching occurs during TLESRs following increased air swallowing during meals and is frequently associated with acid and non-acid symptomatic reflux[72].

Frequency of reflux

The number of reflux events reflects the severity of failure of the antireflux barrier; however, this is not a parameter frequently used for diagnosis of GERD or to evaluate severity of disease. A study that analysed 391 pH-impedance reflux monitoring studies in healthy asymptomatic individuals[73] together with studies of patients with GERD suggest that individuals with <40 reflux episodes in 24 hours do not have GERD, whereas individuals with >80 reflux episodes have GERD and are more likely to respond to antireflux surgery[73–75].

Volume and proximal extent of reflux

It is not currently possible to quantify the volume of the refluxate with the techniques available. However, it is known that reflux episodes with higher proximal extent are often more symptomatic[76]. Impedance-pH studies have shown that symptomatic reflux episodes reach the proximal oesophagus more frequently than asymptomatic reflux[76]. In addition, the proximal oesophagus is more sensitive to chemical and mechanical stimulation than the distal oesophagus, probably due to the presence of more superficial mucosal sensory nerves[77].

Day-to-day variability of reflux and symptoms

Gastro-oesophageal reflux events display a substantial day-to-day variability, probably due to variations in diet, position and physical activities, among others. Unfortunately, 24-hour ambulatory reflux monitoring cannot account for such variability. Prolonged wireless oesophageal pHmetry can detect day-to-day variability of acid reflux[78]. This variability has diagnostic implications and can also explain the intermittent symptomatic days in some patients[79].

Refluxate in patients 'on' PPI treatment

Patients on PPI treatment have mostly weak or non-acid reflux events during the daytime. However, some patients with supine reflux, owing to hiatal hernia, can have supine acid reflux episodes despite being on PPI, suggesting a persistent presence of acid in the stomach owing to partial lack of effect of most PPI treatments during the overnight period (known as 'nocturnal acid breakthrough')[80].

Implications for diagnosis and management

Owing to the contribution of acid reflux to symptoms and mucosal damage, treatment with PPIs should be adjusted to the reflux pattern, for example, twice daily in the presence of supine acid reflux. Furthermore, potassium-competitive acid blockers, a class of acid suppressant agents that inhibit gastric H^+/K^+ ATPase with a faster onset of action than PPI[81], can be considered in those patients suspected of having PPI-refractory reflux. Owing to the day-to-day variability in oesophageal acid exposure and symptoms, prolonged wireless pH monitoring can identify patients with difficult-to-diagnose GERD and provide a guideline for PPI management.

Bile reflux has a major role in the pathogenesis of severe GERD. New bile acid sequestrants are under investigation[82]. In addition, the differential sensitivity between the distal and proximal oesophagus highlights the importance of evaluating the proximal extent of reflux episodes in a pH-impedance test. Patients with a high proportion of reflux reaching the proximal oesophagus are likely to have more-severe typical oesophageal symptoms and/or extra-oesophageal symptoms.

A substantial proportion of patients with GERD have reflux related to belching. In some patients, this is caused by aerophagia during meals followed by postprandial gastric belching. In other patients, reflux is related to supragastric belching. Many of these patients are refractory to PPI treatment. pH-impedance monitoring enables assessment of belching and identification of pathological aerophagia or supragastric belching. For aerophagia and gastric belching, changes in dietary habits and baclofen can be used[56]. For supragastric belching, cognitive behavioural therapy is recommended[83].

Oesophageal clearance after reflux

When reflux reaches the oesophagus, the mucosa is exposed to the refluxate. The duration of exposure and the efficacy of defensive mechanisms determine the severity of GERD symptoms and mucosal damage[84]. The main clearance and defensive mechanisms include: oesophageal motility, which determines the volume clearance; the neutralizing effect of swallowed saliva, which determines the chemical clearance; and the local mechanisms that protect mucosal integrity.

Oesophageal peristalsis and volume clearance

Together with gravity (in the upright position), swallow-induced primary oesophageal peristaltic contractions and oesophageal distension-induced secondary peristalsis can clear most of the volume of refluxate. In patients with GERD, oesophageal body motility can be abnormal (known as ineffective oesophageal motility), contributing to deficient volume clearance[85]. Patients with GERD can have oesophageal hypomotility affecting both primary and secondary peristalsis[86]. Peristaltic dysfunction can be an important contributor to the severity of GERD[85,87].

Swallowed saliva and chemical clearance

After complete clearance of the refluxate volume by peristalsis, the distal oesophageal mucosa remains acidified[88]. Chemical clearance is produced by the neutralizing effects of saliva. Saliva contains bicarbonate, which buffers acid, and epidermal growth factor, which promotes mucosal repair and defences[88].

Reduced salivation, which can result from ageing and use of medication such as anticholinergics or antidepressants, has been associated with prolonged acid clearance times during sleep[89]. Pathological conditions, such as chronic xerostomia (dry mouth), commonly seen in connective tissue disorders, is also associated with prolonged acid clearance and more severe mucosal damage[89].

Post-reflux swallow-induced peristaltic wave

Studies using pH impedance testing have identified a normal reflex that occurs immediately after reflux: post-reflux swallow-induced

peristaltic wave (PSPW)[90]. This is a vagal oesophagosalivary reflex and involves a primary swallow of secreted saliva. This clearing swallow brings salivary bicarbonate, mucin and epidermal growth factor to the distal oesophagus to neutralize pH, repair mucosal damage and reduce risk of long-term acid-related complications. The PSPW is a normal reflex that is present after most reflux episodes in healthy individuals. By contrast, this reflex may not be triggered in patients with GERD, and consequently many of their reflux episodes have abnormal chemical clearance[90].

Implications for diagnosis and management

Evaluating oesophageal motility in patients with reflux symptoms is useful to identify severe oesophageal hypomotility in patients with oesophagitis or Barrett oesophagus and in patients with connective tissue disorders. In addition, it is important to record all the medications that patients consume, especially in older patients. Anticholinergics, antidepressants and opioids can substantially affect oesophageal motility[91]. The tailoring of surgical or endoscopic treatment strategy according to oesophageal motility status remains controversial. Although some gastroenterologists advise partial fundoplication for moderate-to-severe ineffective oesophageal motility, several surgical teams argue that there are no discernible differences in outcomes between partial and complete fundoplication[92].

When oesophageal hypomotility is diagnosed, assessing muscle reserve using the multiple rapid swallow test is clinically relevant[93]. In healthy individuals, after multiple liquid swallows, there is a strong oesophageal peristaltic contraction that clears most of the volume swallowed. In some patients with ineffective oesophageal motility, the absence of an adequate post-multiple-rapid-swallow contraction can be associated with dysphagia after antireflux surgery[93]. Currently, there is no safe and efficient pharmacological prokinetic treatment for oesophageal hypomotility. An abnormal PSPW index during pH-impedance monitoring can be useful for diagnosis of GERD in patients with inconclusive endoscopic and pH-monitoring parameters. Furthermore, it has been suggested that a low PSPW index can predict response to PPI treatment[94].

Oesophageal mucosa

The oesophageal mucosa is a non-keratinized squamous epithelium with three functional layers: a proliferating stratum basalis, with receptors that are stimulated by pro-inflammatory cytokines; a metabolically active stratum spinosum, composed of immune cells (mostly lymphocytes) and epithelial cells connected by tight junction proteins; and a stratum corneum, which is in contact with the oesophageal lumen and includes sensory nerve terminals[95].

Dendritic cells are more abundant in healthy oesophageal mucosa than in GERD phenotypes. A reduced population of mucosal dendritic cells indicates a new pathogenic alteration in the oesophageal mucosa associated with GERD[96].

On the basis of endoscopic findings, it has been established that patients with GERD symptoms and increased reflux can present with non-erosive reflux disease (NERD), erosive reflux disease (ERD) and/or Barrett oesophagus.

Non-erosive reflux disease

The NERD phenotype represents ~70% of patients with GERD[97]. In NERD, substantial evidence exists of specific microscopic alterations, such as microinflammation and dilated intercellular space. In addition, the protective mucus layer is compromised. Functional studies have further validated the decline in the integrity of the oesophageal mucosa in patients with NERD[84,85,98].

These studies have been performed both in vitro (oesophageal biopsy samples) and in vivo (basal impedance)[99]. At the molecular level, intercellular junctional complexes serve to maintain epithelial integrity and enable cell-to-cell transport and signal transmission. Any noxious agent that insults these junctional complexes leads to increased intercellular permeability. The presence of dilated intercellular spaces on electron microscopy has been described as a marker of oesophageal damage in NERD[100]. However, the prevalence and role of dilated intercellular spaces is controversial because they are not specific to NERD and can also be observed in healthy individuals or in patients with eosinophilic oesophagitis[101]. Furthermore, other studies have observed a similar distribution of dilated intercellular spaces in healthy individuals compared with patients with GERD[101,102].

Mucosal integrity depends on intact apical junctional complexes. Tight junction and adherens junctions are formed by several proteins such as claudins and occludins (tight junctions) and cadherins (adherens junctions). Dysfunction of these complexes seems to have a role in the increased permeability of the barrier. Increased oesophageal mucosal epithelial permeability owing to E-cadherin cleavage has been observed in patients with NERD[103].

In addition to dilated intercellular spaces, patients with NERD have changes in oesophageal mucosa innervation and also mucosa microinflammation with elevation of pro-inflammatory cytokine levels in tissue biopsy samples such as IL-8. In biopsy samples from patients with NERD, there are superficial sensory nerves that express TRPV1 and are positioned close enough to the lumen to be activated by H^+ from the refluxate. These nerves are less superficial in the other GERD phenotypes[95,104].

Depending on the results of reflux monitoring (total acid exposure and reflux-symptom association analysis), symptomatic patients with normal endoscopy can have 'true' NERD, reflux hypersensitivity or functional heartburn[74].

Erosive reflux disease

In ERD, it had been assumed that mucosal erosions were the result of cell death caused by acid damage followed by an acute inflammatory response represented by increased mucosal leukocytes that progresses deeper towards the lamina propria, with consequent ulceration. The loss of cells from the oesophageal surface stimulates basal cell hyperplasia, a characteristic histological feature of GERD[105]. However, the acid burn theory has recently been challenged. In studies analysing the histological progression of oesophagitis in both animal tissue and biopsy samples from patients with GERD, it has been shown that before cell death occurs, T cells infiltrate the oesophageal submucosa[106].

This infiltration then extends to the lamina propria and epithelium and triggers the release of chemokines that cause mucosal damage. These findings suggest that the refluxate does not directly cause cell death but instead stimulates an inflammatory chemotactic reaction involving T cells and other inflammatory cells, which ultimately affect the mucosa via the release of chemokines that lead to the mucosal damage[105,106].

In ERD, as well as in NERD, the protective mucus barrier is altered[104]. In patients with ERD, sensory afferent nerves are deeper in the mucosa than in NERD[95,104]. There is an increased number of nerve growth factor-positive mast cells infiltrating the oesophageal mucosa, in close apposition to deep intrapapillary nerves. The basal cell layer is characterized by keratin 14 (KRT14) and KRT17 expression, and there is increased IL-8 secretion by T cells infiltrating the oesophageal epithelium[95,104].

Barrett oesophagus

Barrett oesophagus is a complication of GERD and a risk factor for oesophageal adenocarcinoma. It is produced when the stratified squamous epithelium of the distal oesophagus transitions into columnar cells, that is, metaplasia[107].

The pathophysiology of Barrett oesophagus is not completely understood. There is no agreement on the initiation of Barrett oesophagus, with different theories proposing various origins. These theories include the possibility that it arises directly from the stratified squamous epithelium of the oesophagus or that it originates from the migration of gastric cardiac epithelium cells followed by a process of intestinalization. Some variations of these theories propose that it might stem from a specific cell at the junction of squamous and columnar epithelium, the ducts of oesophageal glands or even from cells derived from bone marrow that circulate in the body[107].

Both short and long segments of the specialized intestinal metaplasia seem to develop through the same pathophysiological mechanisms[108]. As yet, there is not a model that completely mimics the presence of intestinal goblet cells in oesophageal mucosa. Goblet cells reside in the mucosa throughout the length of the small and large intestines and are responsible for the production and maintenance of the protective mucus by synthesizing and secreting high-molecular-weight glycoproteins known as mucins[109]. However, Jiang and colleagues have described an animal model of acid reflux-induced expansion of transitional basal progenitor cells and revealed the presence of a previously unidentified transitional zone in the epithelium of the upper gastrointestinal tract, and provide evidence that $p63^{+}KRT7^{+}$ basal cells in this zone are the cell of origin for Barrett oesophagus[110].

In a transgenic mouse model of Barrett oesophagus, oesophageal overexpression of IL-1β phenocopies human pathology, with evolution of oesophagitis and Barrett-like metaplasia[111]. Both histopathology and gene signatures are very similar to human Barrett oesophagus, with upregulation of TFF2, BMP4, CDX2, NOTCH1 and IL-6 levels. Exposure of the oesophageal mucosa of the transgenic mouse model of Barrett oesophagus to bile acids or nitrosamines accelerated the development of Barrett oesophagus[112].

Implications for diagnosis and management

NERD is diagnosed when there is pathological acid exposure and a normal endoscopy performed after at least 1 week of interruption of PPI treatment ('off' PPIs). New endoscopic parameters using narrow-band imaging can improve diagnosis of NERD. It is clinically important to distinguish true NERD from reflux hypersensitivity and functional heartburn because this can have treatment implications. Mild oesophagitis (grades A and B of the LA Classification)[113] should be managed with standard PPI dosing and does not require follow-up endoscopic controls. Severe oesophagitis (grades C and D) requires PPIs twice daily (also known as 'bid') for 8 weeks and requires endoscopic control at the end of treatment[113].

Approximately 30% of patients with GERD are completely refractory or partial responders to PPI therapy[114]. There are multiple mechanisms involved in refractory GERD, but one of them might be insufficient acid suppression. For this group of patients, a potassium-competitive acid blocker can be an option.

Barrett oesophagus should be managed similarly to patients with GERD – that is, standard PPI dosing to treat reflux symptoms and heal oesophagitis and escalation of dosing for patients with inadequate symptom control. Regarding dysplasia, all clinical guidelines recommend endoscopic ablative therapy for high-grade dysplasia and most of them also extend this recommendation to low-grade dysplasia[115,116].

Perception of oesophageal symptoms

Patients with GERD have substantial interindividual variability in type and severity of symptoms. In patients with confirmed diagnosis of GERD, the severity of symptoms does not correlate with the severity of mucosal damage[117].

Patients with NERD can have similar severity of symptoms to patients with oesophagitis[118]. Furthermore, patients without GERD might perceive their physiological reflux episodes as symptomatic owing to oesophageal hypersensitivity. Finally, some patients have heartburn not associated with a reflux episode or increased acid exposure – that is, functional heartburn[118]. By contrast, other patients, particularly those with morbid obesity, peptic stricture or Barrett oesophagus, have a higher threshold of oesophageal sensitivity (hyposensitivity) and develop severe lesions, with mild or no symptoms[119].

Oesophageal mucosa innervation

In healthy individuals, the location of oesophageal mucosal innervation varies along the oesophagus. In the distal oesophagus, the nerve fibres are predominantly located deep in the epithelium. Conversely, innervation of the proximal oesophageal mucosa seems to be concentrated near the oesophageal luminal surface (superficially)[77]. This has been postulated to be the underlying reason for the increased sensitivity of the proximal oesophagus to reflux. Furthermore, such increased sensitivity of the proximal oesophageal mucosa might contribute to a protective reflex mechanism against tracheal aspiration observed during proximal reflux[77]. There is a differential distribution of mucosal nerve fibres in patients with NERD, ERD and Barrett oesophagus. In healthy individuals and patients with ERD or Barrett oesophagus, the sensory nerves are located deeper in the mucosa. By contrast, patients with NERD have more superficial sensory nerves expressing TRPV1. These nerve distributions can underlie the variable perception of similar stimuli (chemical or mechanical) in the different GERD phenotypes[104].

Central and peripheral neural modulation

Psychoneuroimmune modulation can modify oesophageal sensitivity. Many patients with heartburn have reported that their symptoms get worse when they experience psychological stress[120]. After a night of sleep deprivation, patients with GERD have shown an increased sensitivity to intra-oesophageal acid perfusion[121]. The reflux-induced inflammatory and immune response of the oesophageal mucosa can sensitize the sensory nerves, leading to hypersensitivity[95]. Experimental studies in rats have shown that an acute stress situation can induce dilated intercellular spaces in the oesophageal mucosa[120]. Dilated intercellular spaces have been suggested to contribute to sensory nerve stimulation[120].

Hypervigilance

Another determinant of the severity of the symptoms of GERD and the response to its treatment is psychosocial comorbidities. Oesophageal hypervigilance is a psychological mechanism that leads to heightened awareness and amplification of oesophageal symptoms and sensations[122]. This increased awareness of symptoms generates a learned fear response, resulting in a vicious cycle of autonomic nervous system arousal that leads to unconscious behaviours to avoid the symptom[123,124].

Hypervigilance is present in all phenotypes of GERD regardless of acid load and degree of association between symptoms and reflux episodes, and it is a predictor of symptom severity. Conversely, anxiety levels were not found to be substantially different between GERD phenotypes[124]. Oesophageal hypervigilance might be involved in the pathophysiology of refractory GERD[125].

Implications for diagnosis and management

It is clinically important to correctly distinguish patients with reflux-like symptoms from patients with conclusive diagnosis of GERD. Endoscopy and reflux monitoring, either with wireless pH monitoring or pH-impedance monitoring, can make such a distinction. This is particularly important in patients who are refractory to PPI treatment. Furthermore, it is clinically important to identify the specific GERD phenotype — that is, whether a patient has 'true' NERD, reflux hypersensitivity or functional heartburn — as different GERD phenotypes vary in pathophysiology and treatment.

Given the daily variability in oesophageal acid exposure, we suggest performing prolonged ambulatory monitoring using a wireless capsule to improve diagnostic sensitivity, particularly in patients with intermittent typical GERD symptoms and hypersensitivity to reflux episodes. By contrast, individuals experiencing functional heartburn exhibit symptoms that are not temporally associated with episodes of reflux. Some controversy exists about the inclusion of functional heartburn within the umbrella of GERD[126,127].

Supragastric belching or rumination syndrome are often diagnosed in patients with a previous diagnosis of reflux hypersensitivity. Cognitive behavioural therapy should be considered for these patients rather than use of pain modulators[83,128]. In patients with oesophageal hypersensitivity, there is a central abnormal modulation and a peripheral mucosal neuroimmune alteration[129].

The use of pain modulators and a topical mucosal protection strategy can reduce their symptoms. Given the prevalence and relevance of hypervigilance in patients with oesophageal symptoms, psychological management of hypervigilance is strongly recommended.

Future directions

Our current understanding of the pathophysiological mechanisms of GERD suggests possibilities for further basic and clinical research. From the clinical perspective, it would be important to elucidate distinct pathophysiological mechanisms underlying the different GERD phenotypes. This could enable personalized treatments based on the predominant pathophysiological mechanism of each patient. Understanding the role of the oesophageal microbiota in different GERD phenotypes might explain varying degrees of hypersensitivity, symptom perception and mucosal changes. With respect to basic pathophysiology research, several questions need to be addressed. For example, why do some patients with similar oesophageal mucosal exposure to acid develop erosions and others develop NERD?

Are patients with functional heartburn part of the GERD spectrum? Is the oesophageal mucosal structure in functional heartburn normal? Moreover, an improved understanding of the immune response and microinflammation in NERD and ERD could help the development of specific anti-inflammatory therapies.

From the diagnostic perspective, new techniques could provide more complete diagnostic information, for example, by combining impedance measurements into an endoscopically attached capsule for wireless pH testing. Furthermore, non-invasive diagnostic techniques such as salivary detection of gastric contents could facilitate screening of symptomatic individuals before using empirical PPI treatments. In addition, clinical trials that compare the effect of standard PPI treatment with that of personalized treatment will be critical.

The development of mucosal topical protection strategies could reduce the need for systemic PPI treatments or surgery. Finally, pain modulation through novel pharmacological and specific psychological interventions will enable decreased oesophageal symptom perception.

Conclusions

GERD is the result of multiple pathophysiological mechanisms that lead to an imbalance between protective and aggressive factors (Table 1). It is now recognized that different GERD phenotypes can have different degrees of reflux, composition and volume of the refluxate, and severity of mucosal damage and symptom perception. These variations are probably due to the occurrence of a predominant pathophysiological mechanism in each patient. In this Review, we have described the main pathophysiological mechanisms of GERD and their implications for personalized diagnosis and management (Table 1).

Published online: 04 January 2024

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Acknowledgements
The authors thank A. Ustaoglu, M. Peiris and P. Woodland from the Wingate Institute of Neurogastroenterology, Queen Mary University of London, UK, for sharing their research data (now published) on the role of the oesophageal mucosa in the pathophysiology of GERD.

Author contributions
Both authors contributed equally to all aspects of the manuscript.

Competing interests
D.S. has served as a consultant for Reckitt Benckiser (UK), Jinshan Technology (China) and AlfaSigma (Italy). J.A. declares no competing interests.

Additional information
Peer review information *Nature Reviews Gastroenterology & Hepatology* thanks Ravinder Mittal and the other, anonymous, reviewer(s) for their contribution to the peer review of this work.