Gastro-oesophageal reflux disease

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Gastro-oesophageal reflux disease is one of the most common disorders of the gastrointestinal tract. Over past decades, considerable shifts in thinking about the disease have taken place. At a time when radiology was the only diagnostic test available, reflux disease was regarded as synonymous with hiatus hernia. After the advent of the flexible endoscope, reflux disease was, for a period, equated to oesophagitis. The introduction of oesophageal pH monitoring made us believe that reflux disease could be defined by an abnormally high proportion of time with oesophageal pH less than 4. Moreover, the successive arrival of histamine-2-receptor antagonists and proton-pump inhibitors changed our idea of treatment for the disease, with swings from and towards surgery, endoscopic techniques, and alternative pharmaceutical options.

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Introduction

Reflux of gastric contents to the oesophagus is a physiological event: a healthy person typically has reflux episodes. Gastro-oesophageal reflux disease is defined as reflux that causes troublesome symptoms, mucosal injury in the oesophagus, or both of these.[1] By this definition, oesophageal lesions (erosions, ulceration, intestinal metaplasia) are not needed for a diagnosis of the disease. In fact, most patients with gastro-oesophageal reflux disease show no abnormalities on endoscopic examination. This subgroup is generally said to have non-erosive reflux disease.

The two most typical symptoms of gastro-oesophageal reflux disease are heartburn (pyrosis) and regurgitation. Heartburn is characterised by a painful retrosternal burning sensation of fairly short duration (several minutes). Prolonged oesophageal pH monitoring has shown incontrovertibly that this symptom is indeed generated by the arrival of gastric juice in the distal oesophagus; the interval between reflux event and symptom onset is usually shorter than 1 min. Some patients perceive their reflux episodes as angina-like chest pain. Regurgitation is defined as backflow of gastric content into the mouth, not associated with nausea or retching. Although reflux and heartburn happen predominantly during the day, in particular postprandially, both can also occur during sleep. Nocturnal reflux is associated significantly with severe oesophagitis and intestinal metaplasia (Barrett's oesophagus) and can lead to sleep disturbance.[2] Some patients who complain of heartburn do not have gastro-oesophageal reflux disease; rather, they have a syndrome called functional heartburn.[3]

In addition to the oesophageal symptoms of gastro-oesophageal reflux disease, extra-oesophageal symptoms can occur, such as hoarseness, cough, and asthma. Although evidence is sufficient to support an association between these symptoms and reflux, establishing that an individual patient's extra-oesophageal symptoms are caused by reflux can be difficult. Uncertainty surrounds whether gastro-oesophageal reflux can cause pharyngitis, sinusitis, pulmonary fibrosis, recurrent otitis media, and sleep apnoea.[1]

In developed countries, the prevalence of gastro-oesophageal reflux disease (defined by symptoms of heartburn, acid regurgitation, or both, at least once a week) is 10–20%, whereas in Asia the prevalence is roughly less than 5%.[4,5] In the USA, this disease is the most common gastrointestinal diagnosis to prompt an outpatient clinic visit (8·9 million visits in 2009).[6] The rising prevalence of gastro-oesophageal reflux disease seems to be related to the rapidly increasing prevalence of obesity.

Pathophysiology

Dysfunction of the oesophagogastric junction

Three components make up the oesophagogastric junction: the lower oesophageal sphincter, the crural diaphragm, and the anatomical flap valve. This complex functions as an antireflux barrier.

The lower oesophageal sphincter, sometimes referred to as the intrinsic sphincter, is a 3–4 cm segment of tonically contracted circular smooth muscle at the distal end of the oesophagus. The resting tone of this muscle can vary in healthy individuals, from 10 mm Hg to 35 mm Hg relative to intragastric pressure. Moreover, temporal variation is considerable, with fluctuations happening after meals, activity, and sleep.[7] Reflux can take place when increases in intra-abdominal pressure overwhelm a hypotensive lower oesophageal sphincter (figure 1). However, the most common mechanism for reflux is transient lower oesophageal sphincter relaxations (TLOSRs), which are independent of swallowing. These events are the result of a vagally mediated reflex that is triggered by gastric distension and serves to enable gas venting from the stomach. On average, a TLOSR persists for about 20 s, which is significantly longer than the typical swallow-induced relaxation.[8]

The right crus of the diaphragm forms a sling that surrounds the distal oesophagus, creating a teardrop-shaped hiatal canal. This structure serves as an extrinsic sphincter by augmenting the high-pressure zone of the lower oesophageal sphincter.[9–12] During TLOSRs, temporal loss of crural diaphragm activity happens.[13]

In healthy people, an anatomical flap valve is present at the oesophagogastric junction, which functions to keep the distal part of the lower oesophageal sphincter in the abdomen and to maintain the angle of His (ie, the

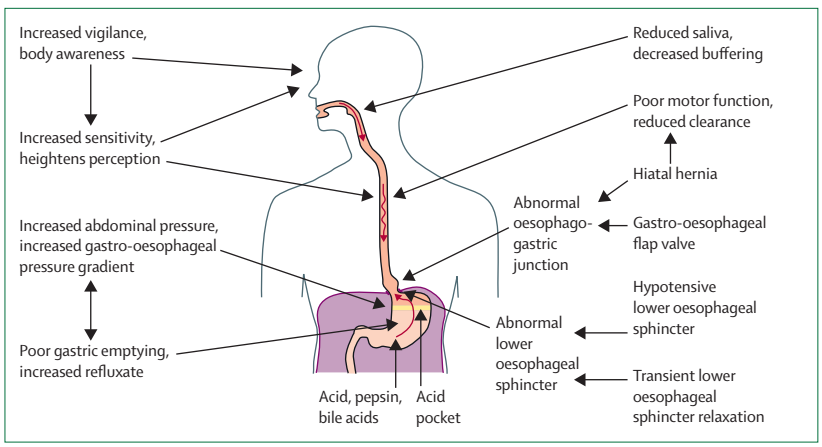

Figure 1: **Pathophysiology of gastro-oesophageal reflux disease**
Dysfunction of the antireflux barrier, increased oesophageal sensitivity, poor motor function of the oesophageal body, and gastric factors (such as raised intragastric pressure and the acid pocket) all play a part.

acute angle between the entrance to the stomach and the oesophagus). Endoscopically, the flap valve can be inspected and graded with the Hill classification (figure 2).[14] As the flap valve disrupts and the lower oesophageal sphincter moves above the crural canal, the high-pressure zone loses its synergistic configuration and both sphincters (lower oesophageal sphincter and diaphragm) become appreciably weaker.[15] The most severe reflux burden occurs when the lower oesophageal sphincter assumes a permanent position above the diaphragm and swallow-associated re-reflux from the hiatal sac impairs oesophageal clearance.[16,17]

Oesophageal body dysfunction

Prolonged acid clearance correlates with both the severity of oesophagitis and the presence of Barrett's metaplasia.[18–20] Acid clearance begins with peristalsis, which empties the refluxed fluid from the oesophagus, and is completed by titration of the residual acid by swallowed saliva (figure 1). Thus, peristaltic function is an important defence mechanism against gastro-oesophageal reflux disease. The relation between peristaltic dysfunction and oesophagitis has been described.[20–22] Of particular importance are failed peristalsis and hypotensive peristaltic contractions (<30 mm Hg), which result in incomplete emptying.[23]

Delayed gastric emptying

In a systematic review,[24] the overall rate of gastric emptying was delayed in patients with gastro-oesophageal reflux disease, compared with healthy controls, the rate being outside the normal range in about a third of patients. However, a relation between delayed gastric emptying and increased reflux could not be seen in that study, suggesting that impaired emptying of the stomach as a whole is not an important determinant of gastro-oesophageal reflux.[24]

Postprandial relaxation of the proximal stomach is augmented or prolonged in gastro-oesophageal reflux disease, and this abnormality is associated with extended presence of the meal in the proximal stomach. A positive correlation was noted between slow proximal—but not distal or total—gastric emptying and oesophageal acid exposure.[25]

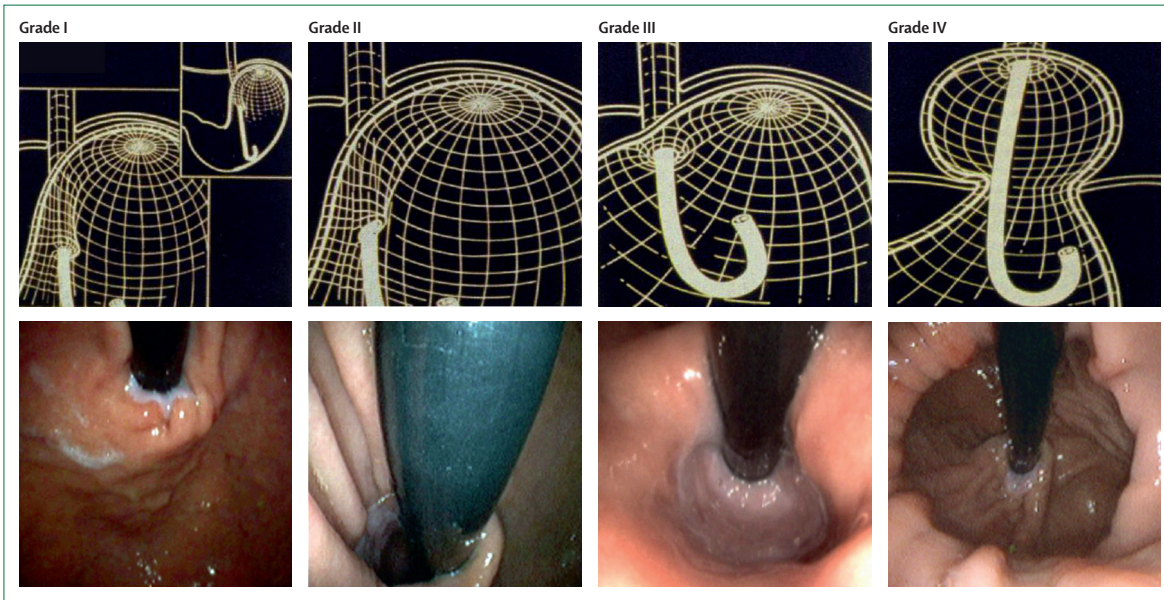

Figure 2: **Progressive anatomical disruption of the gastro-oesophageal junction as it relates to the flap valve antireflux barrier**
(Upper panels) Three-dimensional endoscopic anatomy with endoscope retroflexed. (Lower panels) Endoscopic manifestations of the flap valve grade. Modified from reference 14, with permission of Elsevier.

Increased intragastric pressure

For reflux to take place, pressure in the proximal stomach must be greater than pressure in the oesophagus. The gastro-oesophageal pressure gradient is amplified temporarily during activities that lead to a rise in abdominal pressure (figure 1), such as straining and coughing. A chronically increased pressure gradient is present during pregnancy and in overweight and obese people. Evidence shows incontrovertibly that obesity augments the risk of reflux symptoms, prolonged oesophageal acid exposure, oesophagitis, and Barrett's oesophagus,[26–29] and that increased abdominal pressure is the pivotal mechanistic factor.[30,31]

Acid pocket

Most meals have a buffering effect that leads to reduced acidity of the stomach in the postprandial phase. However, acid reflux (as detected by pH monitoring) is generally most pronounced after meals. In the postprandial period, a layer of unbuffered acidic gastric juice sits on top of the meal, close to the cardia, ready to reflux.[32] This occurrence has become known as the acid pocket (figure 1) and is facilitated by an absence of peristaltic contractions in the proximal stomach.[33] In patients with gastro-oesophageal reflux disease, the acid pocket is located more proximally with respect to the squamocolumnar junction, and it could even extend above the manometrically defined lower oesophageal sphincter.[34] Treatment with alginate-antacid preparations abolishes the pocket or increases the distance between the upper border of the acid pocket and the squamocolumnar junction.[35]

Oesophageal hypersensitivity

In a subgroup of patients with gastro-oesophageal reflux disease, reflux symptoms are noted while oesophageal acid exposure is within the normal range; thus, these individuals are hypersensitive to acid.[36] Hypersensitivity to acid occurs both in people with erosive oesophagitis and in those with a macroscopically normal mucosa (figure 1). Experiments in which acid is infused in the oesophagus indicate that the threshold to development of heartburn and pain is lower in patients with either erosive oesophagitis or non-erosive reflux disease than in controls.[37] Factors contributing to the noted increased oesophageal sensitivity are impaired mucosal barrier function, upregulation of peripheral nociceptors, and central sensitisation.[38–40]

Helicobacter pylori

Helicobacter pylori does not have an important role in the pathogenesis of gastro-oesophageal reflux disease. Eradication of the microorganism does not lead to an increased chance of development of the disorder.[41]

Diagnosis

Endoscopy

Controversy exists about the role of endoscopy to screen for the presence of Barrett's oesophagus in patients with reflux symptoms, and currently, evidence is unclear to support once-in-a-lifetime endoscopy of all patients with gastro-oesophageal reflux disease.[42,43] By contrast, people who present with alarm symptoms (dysphagia, haematemesis, weight loss) warrant endoscopy, because they might have clinically significant complications of gastro-oesophageal reflux disease or other pathological features.[44] For example, the test serves to rule out alternative diagnoses, such as eosinophilic oesophagitis, infection, and pill injury; furthermore, an observation of typical reflux oesophagitis confirms the diagnosis of gastro-oesophageal reflux disease. The severity of endoscopically observed reflux oesophagitis is graded with the Los Angeles classification (figure 3).[45] However, the overall diagnostic yield of endoscopy in gastro-oesophageal reflux disease is low, mainly because most patients with the disease do not have visible erosions in the oesophagus, partly attributable to widespread acid inhibition. Thus, endoscopy is a test with high specificity but low sensitivity for gastro-oesophageal reflux disease.

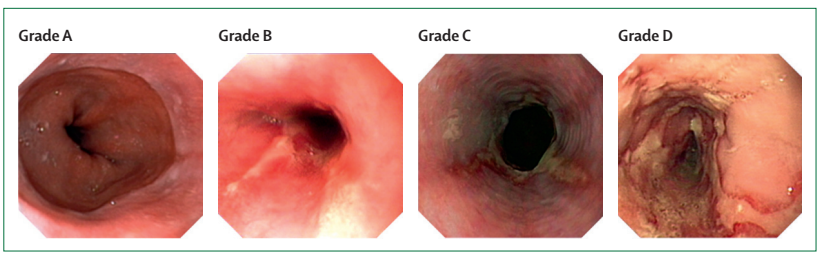

Figure 3: **Los Angeles classification of reflux oesophagitis**
In grade A oesophagitis, endoscopic abnormalities are restricted to one or more mucosal lesions with a maximum length of 5 mm. In grade B, one or more mucosal breaks are present, with a maximum length of more than 5 mm but non-continuous across mucosal folds. In grade C oesophagitis, mucosal breaks are continuous between at least two mucosal folds, but less than 75% of oesophageal circumference is involved. In grade D, mucosal breaks encompass more than 75% of oesophageal circumference.

Proton-pump inhibitor test

The symptomatic response to a short course of treatment with an inhibitor of gastric acid secretion, nowadays invariably a proton-pump inhibitor (PPI), has become known as the PPI test. Generally, a reduction of symptom severity by at least 50% is judged a positive test result and is indicative of a correct diagnosis of gastro-oesophageal reflux disease. However, the PPI test might also be positive in other acid-related disorders, such as peptic ulcer disease and functional dyspepsia, and an important placebo effect has been seen. Therefore, the specificity of the test is poor (24–65%) and is not higher than that of testing with placebo (38–41%).[46] However, in primary care, a short trial of a PPI is deemed useful, because the combination of a favourable response and absence of alarm symptoms makes additional diagnostic testing unnecessary.

Ambulatory reflux monitoring

Conventionally, pH monitoring is done with a transnasally inserted catheter with pH sensor, which is connected to a portable datalogger. Every time acid reflux

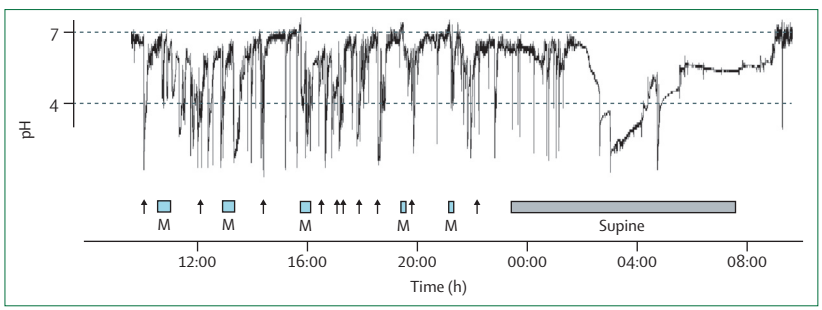

Figure 4: **24-h oesophageal pH monitoring study**
Every drop below pH 4 is interpreted as a reflux episode. Meals (M) and time spent supine are indicated. Onset of reflux symptoms as judged by the patient is marked with a vertical arrow. In this example, 87 reflux episodes were recorded and the total acid exposure time was 15·2%, which is above the upper limit of normal (6%). The patient indicated onset of ten reflux symptoms, eight of which were preceded by a reflux episode, indicating a good relation between reflux and symptoms.

happens a drop in pH is recorded. These measurements are usually taken for 24 h, a period in which the patient is ambulatory and in his own environment (figure 4). Alternatively, a wireless system can be used,[47] whereby a radiotransmitter capsule with pH sensor is attached to the oesophageal wall. The advantage of this technique is that no discomfort is caused by the presence of the naso-oesophageal catheter and prolonged measurement can be done. However, the wireless pH capsules are roughly double the cost of a standard pH catheter.

Oesophageal pH monitoring is generally done after acid-suppressive drugs have been stopped for at least 5 days, otherwise reflux will not be acidic and, hence, not measurable with a pH sensor. The test allows tracking of overall oesophageal acid exposure and, most importantly, investigation of whether or not a temporal relation between symptoms and reflux events is present.[48]

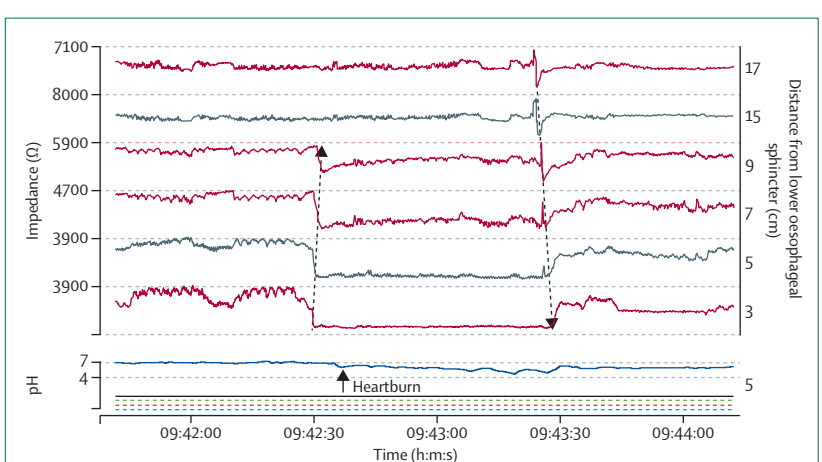

Figure 5: **Combined pH and impedance monitoring to identify non-acid reflux**
Upper traces show intraluminal impedance signals recorded from the oesophagus at 17, 15, 9, 7, 5, and 3 cm from the lower oesophageal sphincter. The lower trace shows pH at 5 cm above the lower oesophageal sphincter. A proximally migrating fall in intraluminal impedance is seen at 09:42:30 h, indicating reflux of fluid (upward dashed arrow). The fluid reaches the electrodes at 9 cm proximal to the lower oesophageal sphincter. This reflux event cannot be distinguished in the pH signal, because pH does not drop less than 4. At 09:43:30 h the refluxate is cleared from the distal oesophagus (downward dashed arrow), undoubtedly by a peristaltic wave.

With pH sensors, only acidic reflux (pH <4) can be detected. However, when antisecretory treatment is used, two-thirds of all reflux episodes are non-acidic, yet these episodes can also trigger reflux symptoms.[49] Oesophageal impedance measurement is a technique that allows detection of reflux independent of the pH of the refluxate. This method uses a catheter with circular electrodes that measure the electrical impedance of the oesophageal contents at multiple levels along the longitudinal axis of the oesophagus. Impedance and pH monitoring are usually done in combination, and a distinction can be made between acid (pH <4), weakly acidic (pH 4–7), and alkaline (pH >7) reflux episodes (figure 5).[50] Reflux events and their association with symptoms such as heartburn can be studied by pH and impedance monitoring while the patient continues to take antisecretory drugs. However, this combined technique is best done off PPIs when the diagnosis of gastro-oesophageal reflux disease has not yet been established and on PPIs when the diagnosis has been made already and the investigation is about why the treatment is ineffective. Combined impedance and pH monitoring has a higher diagnostic yield than pH monitoring alone.[51–53]

Manometry

Oesophageal manometry is not indicated for diagnosis of gastro-oesophageal reflux disease because motor dysfunction associated with abnormal reflux is non-specific. The main indications for manometry are to ascertain the correct position for pH electrode placement and to exclude severe oesophageal motility disorders such as achalasia and absent peristalsis before antireflux surgery.[54] Exclusion of other oesophageal disorders is important, because patients with achalasia can present with heartburn and regurgitation, which could lead to an erroneous diagnosis of gastro-oesophageal reflux disease.[55] However, whether milder forms of peristaltic dysfunction predict postoperative dysphagia is uncertain.[56]

Manometry might be helpful in patients with predominant regurgitation because it can help to distinguish the rumination syndrome from gastro-oesophageal reflux disease. This diagnosis is best accomplished with concurrent pH and impedance monitoring.[57]

Histological analysis

Light microscopy of mucosal biopsy samples in patients with gastro-oesophageal reflux disease can show elongated papillae and hyperplasia of basal cell layers with dilated intercellular spaces.[58,59] Inflammatory cells (including eosinophils) can be present, but pronounced eosinophilia is more indicative of eosinophilic oesophagitis (more than 15 eosinophils per high-power field) than gastro-oesophageal reflux disease. A large interobserver variation, low sensitivity, and low specificity strongly limit the value of histological analysis as a

diagnostic method for gastro-oesophageal reflux disease. Biopsy samples should, therefore, only be taken when other causes of oesophagitis are being considered.

Treatment

Lifestyle and dietary modifications

A common belief is that the first step in management of gastro-oesophageal reflux disease should consist of changes in lifestyle, including diet. Dietary advice is based largely on epidemiological observations showing associations between reflux symptoms and eating habits. High dietary fat intake is associated with increased risk of gastro-oesophageal reflux disease whereas a high fibre intake decreases the risk.[60] However, the effectiveness of dietary recommendations has not been shown, and in view of this absence of evidence, limitation of dietary advice seems wise. Thus, recommendations are to have a generally healthy diet and to avoid food items that, in the experience of the patient, trigger symptoms.

Cessation of tobacco smoking is a sensible recommendation in general, but no data show that stopping smoking leads to a reduction in reflux symptoms. By contrast, much evidence indicates the effectiveness of weight reduction, at least in patients who are overweight or obese.[61,62] The frequent advice to elevate the head of the bed is only rational for patients with gastro-oesophageal reflux disease who have reflux episodes at night. Although symptom-based studies suggest the prevalence of nocturnal reflux is more than 50%, 24-h pH studies indicate that, in many patients, reflux episodes only occur during the day. Findings of a small randomised trial suggest that an induced change (through training) from thoracic to abdominal breathing can improve gastro-oesophageal reflux disease, as assessed by pH, quality of life, and PPI use.[63]

Antacids and alginates

Nowadays, antacids are used mostly in primary care and for self-treatment. Typically, they are used on demand because their onset of action is rapid and their effect short-lived. Depending on the preparation, excessive use of antacids can lead to diarrhoea or constipation and, in patients with renal failure, to hypermagnesaemia or hyperaluminaemia. Alginate is a polysaccharide derived from seaweed. It binds water to form a viscous gum that floats in the proximal stomach, thereby reducing the acid pocket.[35] Commercially available alginate preparations also contain an antacid.

Acid inhibition

Although the pathogenesis of gastro-oesophageal reflux disease depends mainly on anatomical disruption and abnormal motor function, the most reliable medical treatment is based on reduction of acid secretion in the stomach. This approach provides no definite solution: once the drug is discontinued the symptoms will return. With the exception of very rare diseases associated with acid hypersecretion, such as Zollinger-Ellison syndrome, the level of acid secretion in patients with gastro-oesophageal reflux disease is similar to that in asymptomatic controls.[64] Most individuals with mild symptoms occurring less than once a week can be treated with on-demand antacids. Alternatively, standard-dose and over-the-counter histamine-2-(H2)-receptor antagonists can be used for on-demand treatment in patients with non-erosive reflux disease or mild oesophagitis.[65]

In patients with moderate-to-severe symptoms of gastro-oesophageal reflux disease or severe erosive oesophagitis, treatment with PPIs should be regarded as first-line treatment.[66] Findings of many studies show a clear advantage of PPIs over H2 blockers for both healing of oesophagitis and maintenance of healing. Data comparing the various PPIs (omeprazole, pantoprazole, lansoprazole, rabeprazole, esomeprazole) show only small differences between drugs, which are not clinically relevant, across all patients with gastro-oesophageal reflux disease.[67] Individuals not responding to standard-dose PPI treatment might benefit from either a dose increase to twice the standard dose or splitting the dose to a twice-a-day regimen.[68–70] Addition of an H2 blocker at bedtime to PPI treatment enhances the inhibition of nocturnal acid secretion, but this effect wears off within a few weeks.[71]

PPI treatment is very safe. However, over the years, some concerns about the effects of prolonged acid suppression have been raised, including: a high risk of infection; enhanced propensity to develop atrophic gastritis; increased risk of *Clostridium difficile*-associated diarrhoea;[72] greater risk of fractures;[73] hypomagnesaemia;[74] deficiencies of vitamin B12 and iron;[75] and the potential for a transient increase in acid secretion after discontinuation.[76] Clinically important drug interactions are rare. The platelet aggregation inhibitor clopidogrel is less active in conjunction with PPI treatment because of decreased activation. However, recent work suggests that this interaction is not clinically relevant.[77] In patients who need prolonged PPI treatment, the argument to eradicate *H pylori* is not compelling.[36]

Other medical treatment options

Theoretically, treatment with a prokinetic drug that accelerates gastric emptying, increases lower oesophageal sphincter pressure, or hastens clearance of refluxate from the oesophagus could be beneficial in gastro-oesophageal reflux disease. However, the currently available prokinetics metoclopramide and domperidone are not effective for treatment of this disease.[78] Cisapride was an effective drug but is no longer available.[79] New prokinetics are in development.

Most reflux episodes happen during TLOSRs, and these can be inhibited pharmacologically. The γ-aminobutyric acid $(GABA)_B$-receptor agonist baclofen reduces the incidence of TLOSRs and reflux episodes, but this drug is not suitable for treatment of gastro-oesophageal reflux disease because of its central side-effects.[80] Results

of trials with new TLOSR inhibitors are disappointing thus far because of side-effects and limited efficacy.[81]

Reduction of oesophageal (hyper)sensitivity would be a useful approach in patients with gastro-oesophageal reflux disease with low acid exposure and absence of mucosal damage. Data suggest that tricyclic antidepressants and selective serotonin reuptake inhibitors can reduce sensitivity, but evidence is not sufficient to recommend these drugs for use in routine practice.[82,83]

Endoscopic treatment

Currently available techniques for endoscopic treatment of gastro-oesophageal reflux disease include suturing devices, transmural fasteners and staplers, and radiofrequency ablation. Although the techniques all seem feasible and have safety profiles that are similar to those of antireflux surgery, they are not as effective as surgery for returning acid exposure to normal, healing of oesophagitis, and resolution of symptoms. Widespread use of these techniques cannot yet be recommended. Patients considering these procedures should be referred to specialised centres and enrolled in clinical trials.

Surgical procedures

Since publication of the procedure by Rudolf Nissen in 1956,[84] fundoplication has become the gold standard for surgical treatment of gastro-oesophageal reflux disease. Presently, the most common indication for surgery is persistence of troublesome symptoms, particularly regurgitation, in patients with proven gastro-oesophageal reflux disease who have a favourable but incomplete response to PPI. Another frequent reason to choose surgical treatment is the patient's reluctance to use a PPI for the rest of their life. Fundoplication is undertaken infrequently for complications such as intestinal metaplasia, ulceration, or stenosis that develop or persist despite adequate acid suppression.

5-year results of a randomised European trial comparing maintenance PPI treatment (esomeprazole) with laparoscopic Nissen fundoplication[85] showed that the remission rate did not differ between therapeutic strategies. However, at 5 years, acid regurgitation was more prevalent in the PPI group than in the fundoplication group. This disadvantage of conservative treatment was counterbalanced by the finding that dysphagia, bloating, and flatulence were more common in the fundoplication group.

Although the traditional Nissen procedure is a complete (360°) posterior fundoplication, several variants entailing partial or anterior fundoplication have been described and investigated. In recent years, meta-analyses comparing the effects of Nissen and Toupet fundoplication (270°) have been undertaken.[86,87] Both procedures are equally effective with respect to reduction of oesophageal acid exposure and lessening of reflux symptoms, but the Toupet procedure is associated with less dysphagia.

Fundoplication has also proven effective in patients for whom non-acid reflux is an important determinant of symptoms.[88] Fundoplication certainly carries a risk of mortality, but recent figures indicate that 30-day mortality is as low as 0·05% in patients younger than 70 years.[89]

In morbidly obese patients with gastro-oesophageal reflux disease, laparoscopic Roux-en-Y gastric bypass should be considered. This bariatric procedure is highly effective against the disease.[90]

Two alternative laparoscopic antireflux techniques have been trialled. One approach entails placement of a flexible band of magnetic beads around the oesophagogastric junction.[91] The second procedure includes implantation of an electrical stimulator connected to electrodes into the lower oesophageal sphincter.[92] Initial open-label studies of these techniques have yielded encouraging results. However, more information from well-designed comparator-controlled studies with long follow-up is needed before routine use of these procedures can be advised.

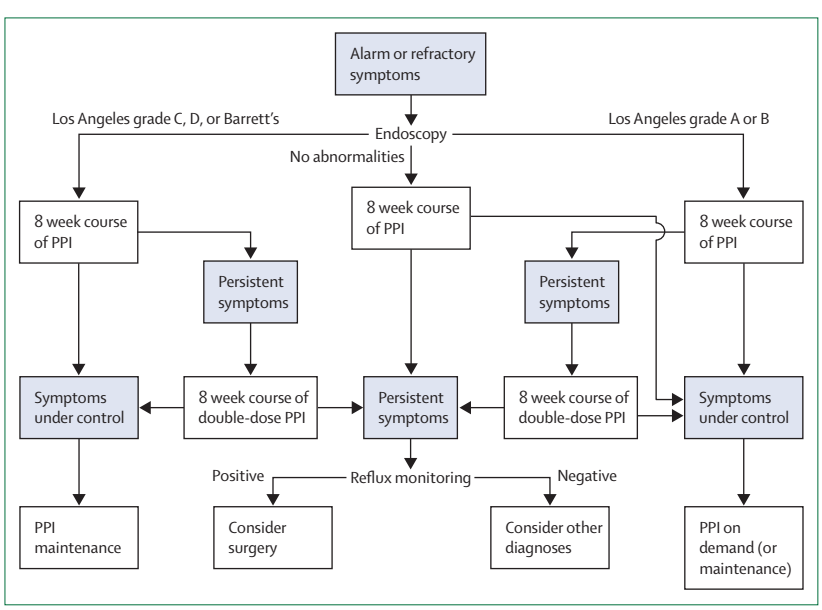

Figure 6: **Management algorithm for symptoms of refractory reflux**

Management

Most patients with gastro-oesophageal reflux disease are treated satisfactorily by lifestyle modifications, antacids, alginates, or acid inhibitors. Figure 6 shows our approach to management of individuals in whom symptoms persist or who present with alarm symptoms. After endoscopy, patients undergo a trial of single-dose PPI, but when this approach has already been tried twice-daily PPI is started. When the response to PPI is satisfactory, patients with severe oesophagitis and Barrett's oesophagus should continue with daily PPI (maintenance treatment) while those with none or mild oesophagitis can use a PPI on demand. When symptoms persist despite a sufficiently long period with high-dose

PPI, the next step is to investigate whether symptoms are truly the result of reflux, using ambulatory reflux monitoring.

Treatment-refractory disease

Treatment-refractory gastro-oesophageal reflux disease is a condition in which symptoms or mucosal lesions caused by reflux of gastric contents are not responding to a high dose of PPI.[93] Data from clinical trials indicate that the efficacy of 4–8 weeks of PPI therapy in healing erosive oesophagitis ranges from 84% to 95% whereas the symptomatic response varies between 75% and 85%.[94–96]

Based on symptoms alone, distinguishing gastro-oesophageal reflux disease from other disorders such as functional dyspepsia and functional heartburn can be difficult.[3] Therefore, the first step in a patient with refractory reflux symptoms is to investigate whether symptoms are truly the result of reflux. Testing can be done with ambulatory reflux monitoring, and outcomes are either that the patient's symptoms are not related to reflux, that symptoms are the result of insufficient acid suppression, or that they are caused by non-acid reflux.

Symptoms not related to reflux

In patients with upper abdominal symptoms of reflux who are refractory to PPI treatment, a diagnosis of functional dyspepsia should be considered. In those with retrosternal burning, the alternative diagnosis is functional heartburn. In both cases, treatment should be redirected.[3]

Insufficient acid suppression

24-h intragastric pH measurements show that inhibition of gastric acid suppression with PPIs is never complete but the remaining acid is usually not sufficient to cause persistent symptoms or erosions.[97,98] Nocturnal acid-breakthrough—a period of at least 1 h in the night with an intragastric pH less than 4—while on a PPI is normal and does not indicate that the drug is ineffective.[99] When pH monitoring during PPI treatment shows very high oesophageal acid exposure, or pH drops to 1 throughout the entire measurement, lack of adherence is usually the cause. Study findings indeed show that 25–47% of people with gastro-oesophageal reflux disease show moderate-to-poor adherence (less than 80% intake of prescribed dose of PPI).[100] Some patients might not be aware that the optimum PPI effect is obtained when taken in advance of a meal. A total absence of effect of these drugs on acid secretion is very rare and is caused by genetic variations in the proton pump.[98] Patients with a gastrin-producing tumour (Zollinger-Ellison syndrome) might also have uncontrollable acid secretion, but gastric and duodenal ulcers are mostly predominant in this disorder. When insufficient acid-suppression happens despite adequate PPI dosing and adherence, anti-reflux surgery could be indicated.

Non-acid reflux

Characteristics of the refluxate other than its acidity—such as the presence of pepsin, bile acids, gas, and its proximal extent and volume—also contribute to symptom perception.[101] PPI treatment reduces the acidity of the refluxate but neither lessens the frequency of reflux events nor decreases the volume of the refluxed material.[53,102] Reflux that is weakly acidic can cause not only regurgitation but also heartburn.[103] Hypersensitivity to oesophageal distension, bile acids, and small falls in pH are likely to have an important role in the perception of non-acid reflux events.[104] Patients with symptomatic non-acid reflux on PPI treatment are judged good candidates for antireflux surgery.

Extra-oesophageal reflux manifestations

Treatment of extra-oesophageal reflux manifestations, such as laryngitis, hoarseness, globus, cough, and asthma, is similar to that for oesophageal complaints, with the general caveat that the therapy is most likely to be successful in the context of concurrent oesophageal symptoms, such as heartburn and regurgitation. The reason behind the lower response rate for extra-oesophageal symptoms could be that many patients have an alternative diagnosis, and reflux is not the cause of their symptoms. No gold standard for diagnosis exists and, thus, management is usually led by clinical suspicion, response to empirical trials, and borderline morphological abnormalities.[105] Empirical trials are advocated by the American Academy of Otolaryngology and Head and Neck Surgery,[106] whereas they are discouraged by the American Gastroenterological Association[66] unless concomitant oesophageal syndromes are noted.

Complications

Peptic stricture

A peptic stricture is the result of the healing process of erosive oesophagitis, whereby collagen deposition and fibrosis lead to narrowing of the oesophageal lumen. In addition to peptic injury, the differential diagnosis should include eosinophilic oesophagitis, malignant disease, dermatological diseases (epidermolysis bullosa dystrophica, lichen planus), and caustic injury. Presentation might be associated with typical symptoms of gastro-oesophageal reflux disease, such as heartburn and regurgitation; however, patients can also present with dysphagia and food impaction without symptoms of gastro-oesophageal reflux disease. The approach to treatment depends on the cause and characteristics of the stricture and usually includes acid suppression, with at least daily PPI, and dilation therapy.[107] The choice of dilator (bougie or balloon) depends on the experience of the endoscopist; most strictures can be managed with either. Complicated strictures might need a combination of approaches and repeated sessions. Refractory strictures are those not responding

to repeated sessions (usually three). An intralesional steroid injection or placement of an endoprosthesis might be needed in such cases; however, data for these techniques are limited.[108,109]

Barrett's oesophagus

Barrett's oesophagus is a complication of gastro-oesophageal reflux disease in which potentially precancerous metaplastic columnar cells replace the normal squamous mucosa. Management of Barrett's oesophagus is both complicated and controversial, as shown by conflicting recommendations from the British Society of Gastroenterology[43] and the American Gastroenterology Association.[42] Even the definition of Barrett's oesophagus is unclear, with British guidelines accepting macroscopic evidence of columnar metaplasia whereas pathological findings of intestinal metaplasia are required in US guidelines. Regardless of the different definitions, both British and US guidelines recognise the malignant potential of the disease and the requirement to survey patients who have Barrett's oesophagus. Some mild differences are noted in surveillance protocols. The American Gastroenterology Association supports intervals of 3–5 years if no evidence of dysplasia is seen and a shorter interval for low-grade dysplasia (6 months) and high-grade dysplasia (3 months or intervention). The British Society of Gastroenterology recommends an interval of 2 years if no evidence is seen of dysplasia, 6 months for low-grade dysplasia, and intervention for high-grade dysplasia (if feasible). In terms of intervention, both organisations recognise that endoscopic ablation is a viable option for some patients with high-grade dysplasia. However, data for endoscopic ablation in Barrett's oesophagus without dysplasia is not supported by evidence.

Conclusions

Gastro-oesophageal reflux disease is very common, defined as symptoms or mucosal damage as a result of reflux of gastric contents into the oesophagus. The spectrum of gastro-oesophageal reflux disease is broad, encompassing not only reflux oesophagitis and Barrett's oesophagus but also non-erosive reflux disease. Diagnosis can be difficult with non-erosive reflux disease. The cornerstone for treatment of all manifestations of gastro-oesophageal reflux disease is acid suppression with a PPI. Lack of response to acid inhibition suggests the diagnosis of gastro-oesophageal reflux disease is incorrect or that the patient is not adhering to treatment and should not prompt a further increase of the PPI dose but rather lead to reconsideration of diagnosis. Reflux monitoring, preferably by combined pH-impedance measurement, is a very helpful diagnostic technique in these patients.

Contributors

All authors contributed equally to the ideas in this paper, the literature search, data interpretation, writing of the manuscript, and construction of the figures.

Conflicts of interest

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