Clinical gastroenterology

A practical problem-based approach
This edition of *Clinical Gastroenterology* is dedicated to the late Christopher J Martin, Foundation Professor of Surgery, University of Sydney at Nepean Hospital, 1993–2006. Chris was a world-class oesophagologist and gastrointestinal surgeon; the Whiteley–Martin Research Unit at Nepean Hospital, which studies upper gastrointestinal cancer, was named after him.
Foreword

It is a great honour and privilege to write the Foreword for the third edition of *Clinical gastroenterology: a practical problem-based approach*, edited by Professor Nicholas J Talley. This book has proven to be a wonderful addition to our educational repertoire in gastroenterology. A myriad of books and educational electronic tools (e.g. Up-to-Date) exist to help the practitioner with disease-oriented questions. However, very few educational media bring us back to the patient. In this wonderful book, Professor Talley and colleagues focus on symptom-based medicine. After all, it is symptoms and the sense of feeling unwell which brings patients to the practitioner for relief and improvement in their health. In our current era of applying a barrage of imaging and endoscopic technologies to patient’s problems, we often lose track of a rational and symptom-based approach in evaluating a patient’s symptoms. Indeed this is one of the few books to address these issues from a presenting complaint perspective.

In addition to its erudite approach to the patient, this book also employs problem-based learning methodology. This is a highly successful educational tool to improve recognition and retention of medical information. It takes a great deal of care and foresight to develop an educational forum using this approach. Again, Professor Talley and his colleagues have done a remarkable job of incorporating the problem-based learning approach into all of their chapters. His team of largely Australian doctors and colleagues with whom he has interacted in the Mayo Clinic system in the United States of America have done a really stellar job in adhering to the goals and objectives of this learning approach. Obviously the success of this book is highlighted by the need for a third edition. From my perspective this book will ultimately be used worldwide by medical students and practitioners trying to understand the relationship between symptoms and pathophysiological processes in gastrointestinal diseases. Professor Talley and his colleagues simply need to be congratulated on helping to promote outstanding education in gastroenterology!

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18 November 2010
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Preface

‘We expect too much of the student and we try to teach him too much. Give him good methods and a proper point of view, and all other things will be added, as his experience grows.’ Sir William Osler

Welcome to the 3rd edition of Clinical gastroenterology: a practical problem-based approach! The last edition was published in 2006, and it is very gratifying to see its success translate into another edition so soon. The production of a 3rd edition of a textbook normally indicates it has survived childhood and adolescence and has reached adulthood, reflecting its acceptance as a valuable education tool. The editor and authors have strived to ensure that this new edition remains a learning gem.

The aim of the book is unchanged: to provide an up-to-date, systematic, highly integrated yet very practical account of gastroenterology, hepatology, endoscopy and gastrointestinal surgery. With this in mind, the book retains its clinical focus, starting with a common (or uncommon but important) problem, and working through the assessment, differential diagnosis, pathophysiology and management, complementing a problem-based learning approach now so popular around the world.

A number of new features have been added in this edition. Each chapter now starts off with a case to set the scene and illustrate some essential principles. At the end of each chapter is a list of key points to promote learning, followed by a list of current, important references. Every chapter has been carefully revised and edited to ensure the material is current, reflects best practice and is easy to understand. A new two-colour layout enhances the readability of the text and tables. Five new chapters have been added covering when to test and treat Helicobacter pylori, inflammatory bowel disease, obesity, preparing for endoscopy and sedation, and management of end-stage liver disease and liver transplant.

This is an international textbook with contributors from Australia, Europe and the USA, all of whom are experts in the field; I remain very grateful for their efforts. We have relied on feedback from peer reviewers and readers as we have prepared this new edition; please do not hesitate to contact us with your suggestions and recommendations.

We have missed the input of the late Professor Christopher Martin into this edition, but believe the book will live up to his high standards.

Gastroenterology is an exciting hands-on specialty that has seen very considerable advances over the past few decades. Whether you are a medical student, resident, registrar or general practitioner, this volume will provide valuable management guidance when you next encounter a particular gastrointestinal symptom, sign, laboratory test or x-ray.

Nicholas J Talley
Newcastle, December 2010
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Case
A 52-year-old male presents with intermittent, retrosternal burning. This tends to occur after meals, but occasionally is worsened by exercise. He gets relief with drinking water and with antacids. The symptom has been present for years, but has become progressively more severe over the past 6 months. He has also developed what he describes as ‘slow swallowing’, which on further questioning sounds like mild dysphagia to solids that happens about once a week. He has gained 10 kg in the past year and has no evidence of gastrointestinal bleeding. His examination is unremarkable except for mild obesity (BMI = 31) and his stool has no occult blood. He had a normal exercise stress test as part of a recent executive physical.

He is started on omeprazole 20 mg daily and scheduled for an upper endoscopy due to his dysphagia and duration of disease. The endoscopy is performed after he was on the omeprazole for 4 weeks and demonstrates a 3 cm hiatal hernia with a lower oesophageal ring of about 15 mm diameter. There is no evidence of Barrett’s oesophagus. Dilation is performed to 20 mm. On follow-up questioning, he states that his reflux symptoms are 90% improved on the omeprazole and his dysphagia has resolved. He is counselled on dietary changes including, most importantly, smaller meals with lower fat content with a goal to improve both his weight and reflux symptoms. In 4 months, he returned with recurrent symptoms after stopping his omeprazole. He was counselled that he probably would need long-term maintenance, and the surgical and medical options were reviewed. He elected to remain on omeprazole and quickly became asymptomatic.

History
‘Indigestion’ is a commonly used but poorly understood term that means different things to different patients. Careful questioning may allow the examiner to determine if the patient is describing heartburn, acid regurgitation, belching, bloating, abdominal pain, halitosis or even flatus. Some patients even use the work ‘gas’ to describe indigestion.

Heartburn, regurgitation and, to a lesser extent, chest pain are symptoms that imply oesophageal disease. The type of oesophageal disease responsible for these symptoms can often be anticipated on the basis of history alone. Physical examination rarely contributes to the diagnosis. Heartburn and regurgitation will be discussed together as they often co-exist in patients with gastro-oesophageal reflux disease (GORD). Chest pain does not imply a particular disease process, but rather a group of disorders and will be discussed separately.

In this chapter, the features of and approach to symptoms best described as heartburn and regurgitation will be outlined and associated symptoms supporting the diagnosis of GORD and its complications will be discussed. Thereafter, a practical guide to the use of investigations to confirm the clinical diagnosis will be presented as well as an outline of the principles of clinical management. Similarly, a practical approach to the diagnosis and management of chest pain will be discussed.

Heartburn
Heartburn is a pain or discomfort typically described as burning in nature. Its primary position is usually lower retrosternal, deep to the xiphisternum. Heartburn commonly radiates upwards, retrosternally, occasionally as far as the neck. There may be associated epigastric pain.

The timing of heartburn is characteristic. It occurs intermittently, either postprandially or when the patient bends forward or lies flat in bed, when the gastric contents are level with, or above, the lower end of the oesophagus. When it occurs
postprandially, it is most commonly in the early postprandial period, 5 to 30 minutes after a meal. The postural changes that initiate heartburn do so by raising the level of the gastric contents above the level of the gastro-oesophageal junction. The duration of an individual attack, when untreated, rarely exceeds an hour.

Factors that precipitate an attack vary considerably from patient to patient. For some, the size of the meal is important, such that it will occur with large meals but not small meals. For others, particular foodstuffs will precipitate an attack. Foodstuffs more commonly incriminated include curries, garlic, red wine, fatty foods, chocolate and citrus juice. The combination of a meal and lying down can be additive in effect. Some patients will describe waking from sleep with severe heartburn a few hours after retiring to bed, particularly following dietary indiscretions. Attacks may occur when the patient lies on the right side but not on the left side or supine. Exercise, either isometric, including straining, or isotonic, such as brisk walking or running, can trigger heartburn. Retrosternal burning pain that is triggered by exercise needs to be closely scrutinised to ensure that symptoms of coronary ischaemia are not being overlooked.

Response to medication is often predictive of whether the patient's complaints are secondary to GORD and, therefore, qualify as heartburn. Retrosternal burning pain that is not at least partially relieved by appropriate medication is unlikely to be caused by the reflux of acid into the oesophagus, unless there is some other strong evidence supporting reflux as the cause of the symptom. Heartburn is usually relieved within several minutes by antacids. Discomfort relieved within much shorter periods or after much longer periods is less likely to be secondary to gastro-oesophageal reflux. Similarly, heartburn usually improves with agents that diminish gastric secretion of acid such as H₂-receptor antagonists and proton pump inhibitors, although relief with these agents is not as immediate as the relief produced by antacids.

The time course, severity and frequency of heartburn will vary considerably from patient to patient. Some patients have the recent onset of symptoms, while others will have symptoms dating back over many years; some describe symptoms as occasional only, while others are inconvenienced many times a day. It is important to ask about nocturnal symptoms since those patients may have more severe mucosal disease, a poorer health-related quality of life and more difficult to treat disease. Heartburn is very common, reported by one-third of the population at least once a month; 10% have daily heartburn. Only a minority of those with reflux symptoms present for medical care.

Regurgitation
Regurgitation is the second ‘typical’ symptom of GORD. Patients with regurgitation often, but not always, also have heartburn. Although the two symptoms can be closely linked temporally, heartburn tends to be more frequent.

Regurgitation describes the intermittent, sudden and often spontaneous sensation of material moving from the stomach proximally towards the oesophagus and throat. Individual patients tend to regurgitate about the same volume of bolus each time. The usual precipitants of heartburn for a particular patient are also the precipitants of acid regurgitation. They include meals (especially larger meals), assumption of a horizontal posture, rises in intraabdominal pressure, and belching. Food regurgitation is described as the predominant form of regurgitation by some patients. This will obviously occur mostly after eating. Regurgitation occurring within the first 30–60 minutes after a meal usually will not be acidic in character, while regurgitation occurring more distant in time from a meal will usually be acidic. Regurgitation may persist in a treated patient even if the heartburn has resolved with acid suppression.

‘Waterbrash’ is a term used to describe the sudden appearance of a volume of salty or tasteless fluid in the mouth. It is the result of salivary gland stimulation in response to gastro-oesophageal reflux or peptic ulcer disease. At times, it is difficult to distinguish from regurgitation, but since both are reflux symptoms, that distinction is not always critical. There are several other symptoms that can be confused with regurgitation. Rumination is the effortless return of food into the oesophagus or mouth. This usually occurs during meals and the food is often reswallowed. Patients with bulimia are also occasionally misdiagnosed as having GORD. Finally, burping and belching involve the ‘reflux’ of air, not liquids, and can also be confused with regurgitation. Patients with rumination, bulimia and aerophagia (excessive belching and burping) can usually be diagnosed with a carefully taken history and will, at times, have false positive ambulatory reflux testing.

Complications of acid regurgitation
Severe acid regurgitation can be associated with other problematic symptoms including choking attacks, cough, asthma, hoarseness of voice, a foul taste in the mouth in the morning, bad breath, a
Heartburn, regurgitation and non-cardiac chest pain

sore tongue, dental caries and nasal aspiration. Some patients complain of waking up episodically with a sensation of choking such that they will cough vigorously, but rarely produce sputum, get up out of bed and even go to an open window to catch their breath. These symptoms subside fairly rapidly. For some, the history suggesting episodic tracheal aspiration will be less dramatic. They may describe a chronic cough, perhaps worse in the morning, but without sudden exacerbations. When that is the case, other causes of cough will need to be considered and excluded as part of a respiratory work-up. Asthma usually has an allergic basis but, occasionally, can be precipitated by gastro-oesophageal reflux. Such patients may present later in life without any obvious cause for obstructive airways disease. In these patients, the symptoms of gastro-oesophageal reflux are commonly not severe. Acid regurgitation can result in a chemical laryngitis and cause hoarseness of voice. Usually the regurgitation occurs at night so hoarseness is most evident in the morning and gradually settles as the day passes. Similarly, waking up with a foul taste in the mouth or bad breath can be attributed to nocturnal gastro-oesophageal reflux. Nasal aspiration is a particularly unpleasant consequence of regurgitation, again usually occurring at night.

Problems with swallowing

Odynophagia
GORD is one of the causes of odynophagia (pain on swallowing). It is usually reported in response to hot or cold foodstuffs (see Ch 2).

Dysphagia
The sensation of obstructed swallowing is unusual in patients with heartburn and regurgitation and, when present, is worthy of special clinical attention. Oesophageal stenosis secondary to severe, long-standing erosive peptic oesophagitis is the most common cause of reflux-induced dysphagia. An undiagnosed oesophageal carcinoma should be considered in appropriate clinical settings. It is the implied severity of the reflux disease and the possibility of malignancy that makes investigation by barium swallow and upper gastrointestinal endoscopy mandatory in these patients. The features of dysphagia usually associated with a benign stenosis secondary to peptic oesophagitis are:

● exclusively for solids (not liquids);
● experienced at the lower end of the sternum;
● little variation in severity from day to day given the same-sized bolus;
● slow progression in severity over months to years; and
● minimal to no weight loss.

There are patients with symptoms of dysphagia and reflux for whom an organic cause will not be found by endoscopy or barium swallow; dysphagia in these cases may be caused by a motor disorder of the oesophageal body. It is usually not clear whether this dysmotility is due to chronic reflux or if motility is the primary problem. If confirmation is required (after more serious disease has been excluded by barium testing or endoscopy), an oesophageal manometry and ambulatory reflux test may be required. Alternatively, resolution of dysphagia after a trial of proton pump inhibitor therapy is nearly diagnostic of a reflux association.

Examination
A typical history of heartburn or acid regurgitation is usually sufficient to diagnose GORD. There are no specific signs on physical examination that support the clinical diagnosis. Deep epigastric tenderness may be present, but is not specific and is not of any particular clinical significance. The role of the examination in GORD is mainly to exclude other issues such as pulmonary disease, cardiac auscultation abnormalities and severe tenderness (unlikely to be present with GORD).

Pathophysiology of GORD
The oesophagus and the stomach are separated by a high-pressure zone produced by tonic contraction of specialised smooth muscle of the lower oesophageal sphincter (LOS) and the phasic contraction of the diaphragm. In normal individuals, this functional barrier is maintained except to allow antegrade flow with swallowing and retrograde flow with belching and vomiting. Reflux is likely when the LOS has a very low basal pressure. In patients with a weak sphincter, increases in intraabdominal pressure can easily overcome that pressure and produce pathological amounts of reflux. On the other hand, most patients with reflux have relatively normal pressure and it is felt that the LOS tends to relax at inappropriate times, leading to reflux (transient LOS relaxations). Hiatus herniation predisposes to reflux as a result of a dissociation of a weak LOS with the added pressure provide by the diaphragm. In addition, a hernia predisposes to inadequate clearance of gastric contents away from the lower oesophagus.

Most of the fluid volume of refluxate is promptly cleared from the oesophagus by one or more swallows. Small amounts of residual acid are neutralised by
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weakly alkaline saliva with subsequent swallows. Clearance is delayed during sleep when swallowing is less reliably triggered by reflux. Smoking exacerbates the effects of reflux by inhibiting salivation, thereby delaying acid clearance.

Repeated and prolonged exposure to gastric secretions can result in erosion and ulceration of the oesophageal mucosa. The occurrence of injury, expressed as erosive oesophagitis, is dependent on three factors: (1) duration of exposure; (2) the chemical composition of the refluxate; and (3) the natural resistance of the individual. Thereby, we can explain several well-known clinical observations. First, the severity of oesophagitis tends to be worse when oesophageal acidification is prolonged, and reducing gastric acid secretion promotes healing of peptic oesophagitis. Secondly, two patients with similar levels of reflux, as measured by pH monitoring, may have marked differences in mucosal appearance at endoscopy. One may have severe erosive oesophagitis while the other, a normal-looking mucosa. The role of bile and pancreatic juice in producing oesophagitis in patients with an intact LOS and pylorus is limited. This mechanism is of considerable importance in patients without an intact pylorus.

Heartburn, on the other hand, is dependent primarily on mucosal sensitivity, not mucosal ulceration. Thus, some patients with symptomatically severe heartburn may have no peptic oesophagitis, while others with no heartburn can present with a peptic stricture secondary to long-standing peptic oesophagitis. Therefore, the severity of heartburn is a poor predictor of oesophagitis. This is a particular problem in older patients who often present with advanced oesophageal damage despite relatively modest symptoms.

Investigation of Heartburn and Acid Regurgitation

Upper gastrointestinal endoscopy
The finding of peptic oesophagitis at endoscopy confirms that symptoms of heartburn and regurgitation are due to GORD. On the other hand the absence of oesophagitis in no way excludes GORD. Patients with typical symptoms that occur occasionally and that are completely controlled by simple measures, such as attention to lifestyle (see below) or antacids, do not need upper endoscopy. On the other hand, patients with reflux symptoms and alarm features (such as vomiting, bleeding, weight loss or dysphagia) should always be investigated. In addition, certain patients (particularly older patients with chronic symptoms) should undergo endoscopy to screen for Barrett’s oesophagus.

The characteristic endoscopic signs of reflux oesophagitis are shown in Table 1.1 and Figure 1.1. As mentioned above, there is only a weak correlation between the severity of oesophageal acidification and the degree of peptic oesophagitis. On the other hand, it is clear that more severe grades of oesophagitis are more difficult to heal. Oesophagitis should never be diagnosed based on anything short of mucosal erosion and never should be based on erythema of the distal oesophagus. The diagnostic endoscopic examination is always carried as far as the first part of the duodenum looking for incidental pathology. The finding of a

<p>| Table 1.1 Classification of reflux at endoscopy (Los Angeles—LA—System) |
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<th>Grade</th>
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<td>Grade A</td>
<td>At least one mucosal break (erosion) each $\leq 5$ mm</td>
</tr>
<tr>
<td>Grade B</td>
<td>At least one mucosal break $&gt; 5$ mm but not continuous between the tops of two mucosal folds</td>
</tr>
<tr>
<td>Grade C</td>
<td>At least one mucosal break that is continuous between the tops of 2 mucosal folds, but which is not circumferential ($&lt; 75%$)</td>
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<tr>
<td>Grade D</td>
<td>Circumferential mucosal break ($\geq 75%$)</td>
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Figure 1.1  Endoscopic view of linear erosive peptic oesophagitis (Grade D) of the distal oesophagus. From plate 20–4 of the online edition of the Merck Manual, with permission from Dr D Martin.
chronic duodenal ulcer is significant as this may be the underlying cause of gastro-oesophageal reflux symptoms (see Ch 5).

**Oesophageal biopsy at upper gastrointestinal endoscopy**

Biopsy of a normal-appearing oesophagus was once suggested to aid in the diagnosis of GORD, but is not advocated by most experts in adult GORD. Microscopic changes suggestive of GORD include:

- relative increase in papillary height;
- relative increase in thickness of the basal layer of the epithelium;
- the presence of intraepithelial neutrophils and eosinophils.

These microscopic findings can be relatively difficult to quantify on routine biopsy specimens and the diagnostic value of these findings continues to be disputed, so biopsy is not recommended routinely. Recently, some experts have suggested obtaining mideosophageal biopsies in patients with any unexplained oesophageal symptom (especially dysphagia) to search for histological evidence of eosinophilic oesophagitis (Ch 2).

**Upper gastrointestinal radiology**

Before the establishment of flexible upper gastrointestinal endoscopy, upper gastrointestinal contrast radiology with barium was the initial investigation for dyspepsia and reflux symptoms. It has been downgraded to a second-line investigation, mainly because it is not a sensitive detector of oesophageal mucosal damage. It does, however, offer complementary information, which is sometimes useful. Some advocate routine radiological testing in any patient with dysphagia. It also allows better definition of the presence and size of a hiatus hernia, which may be important if surgery for reflux is contemplated. The demonstration of barium refluxing into the oesophagus is neither specific nor sensitive for the presence of pathological acid reflux.

**Ambulatory reflux monitoring**

Episodes of gastro-oesophageal reflux result in acidification of the distal oesophagus. Neutral pH is restored by oesophageal peristalsis. These episodes can be monitored and recorded by placement of a pH microelectrode in the distal oesophagus. In the past this test required prolonged nasal intubation, which is unpleasant. That discomfort can now be avoided by attaching the pH electrode to the lower oesophageal mucosa endoscopically. The pH recording then occurs by telemetry. The electrode subsequently detaches and passes spontaneously.

Summation of the duration of episodes over an extended period, usually 24–48 hours, gives a measure of the underlying pathophysiological process, which can be used to score the severity of the disease. Further, a correlation between symptoms and episodes of oesophageal acidification can be established (see Fig 1.2). The test is not required for diagnosis in the majority of patients with typical symptoms of reflux in whom the diagnosis can be made either endoscopically or, if there is no oesophagitis, on the basis of a successful therapeutic trial with a course of antisecretory treatment.

Recently, another technology has been developed that has the potential to measure not only acid reflux, but also the reflux of other substances with a more neutral pH. This technology takes advantage of the conductivity of refluxed liquid and is measured with a specially designed catheter that not only measures the movement of that fluid using impedance, but also measures pH (acid reflux). The exact role of this testing remains to be completely defined, but has been suggested to be of particular benefit in patients requiring testing while on acid suppression.

When contemplating performing an ambulatory reflux test, two questions must be answered: should the test be done on or off acid-supression therapy and should impedance monitoring be included? Off-therapy testing is the best way to determine if the patient has pathological gastro-oesophageal reflux. This testing can be performed with either a tube-based or tubeless system. If, on the other hand, the question is of ongoing reflux on therapy, some experts advocate a combined impedance pH test. An alternative, especially in the patient with either no or a modest response to therapy, is to stop medications and do a pH test off therapy. The application of the concept of pretest probability is important in that decision-making process. If the patient is believed to have reflux and a non-acid contribution to symptoms is to be excluded, on-therapy, impedance pH testing makes sense. If on the other hand, the patient is not believed to have reflux (often the case when there is a minimal response to therapy), stopping therapy and doing an off-therapy test is most reasonable. A negative off-therapy pH test and a failed therapeutic trial provide the best evidence that reflux is not the cause of an individual patient’s symptoms.

**Bernstein testing**

Bernstein testing is a test of mucosal sensitivity that is of mostly historical interest, although it may be available in a few referral centres. It involves transnasal oesophageal intubation and perfusion...
Figure 1.2
Heartburn, regurgitation and non-cardiac chest pain

of the distal oesophageal mucosa with dilute (0.1 M) hydrochloric acid alternating with placebo (normal saline). The test is considered positive if the acid produces the patient’s symptoms and the saline does not. It can be complementary to pH monitoring in patients whose atypical symptoms, particularly chest pain, are infrequent and do not occur during a pH-monitoring study.

Oesophageal manometry

This test has no routine diagnostic role in the evaluation of symptoms of GORD unless antireflux surgery is being considered, where manometry is used to exclude achalasia and to tailor the tightness of the repair. It may sometimes be useful in the evaluation of patients with symptoms of dysphagia in addition to those of heartburn and regurgitation, where a barium swallow and endoscopy have been normal and the dysphagia remains unexplained (see Ch 2).

Treatment

Clinical management of heartburn and regurgitation

The intensity of reflux symptoms varies from a mild, occasional discomfort, for which the patient may want little more than antacid and reassurance, to a daily, incapacitating pain that prevents normal activity. Management needs to be commensurate with the magnitude of the clinical problem. Unlike duodenal ulceration, GORD is usually a persistent condition without exacerbations and remissions. Drug therapy has a hierarchy (see Box 1.1). Oesophagitis indicates a need for therapy to heal the mucosa and maintain healing; virtually all patients with severe oesophagitis (LA grade C and D oesophagitis; see Table 1.1) will relapse if medical therapy is stopped, as will most (80%) with milder oesophagitis. A review of the clinical management principles for patients with gastro-oesophageal reflux is presented in Table 1.2.

Patient-directed therapy

For most of the population who have occasional, mild symptoms of reflux, intermittent, patient-directed treatment is all that is required. Such treatment involves lifestyle changes including:

- weight loss, if overweight or in the face of recent weight gain;
- avoidance of large meals, particularly before retiring to bed at night;
- postural advice including elevation of the head of the bed by insertion of 20 cm blocks under the bed head and avoidance of bending;
- avoiding drugs, cigarettes, alcohol and foodstuffs that might precipitate reflux.
A foodstuff checklist includes spicy foods, alcohol, fatty foods, chocolates, nuts, tomatoes, as well as many others. Rather than prohibit ‘everything’ and risk losing patient compliance, it is wiser to establish with the patient which foodstuffs they recognise as triggers, ask them to avoid these, go through the checklist to identify triggers that the patient might not have previously considered and recognised, and then ask the patient to establish relationships between symptoms and triggers so that they might be avoided in the future. In addition, some aspects of the ‘reflux diet’ such as lower volume, lower fat and weight loss will provide added health benefits beyond the improvement in reflux symptoms.

Of these various lifestyle changes, only weight reduction has the potential to change the natural history of the disease. Thus, some patients can clearly identify a critical weight above which they experience symptoms and below which they are free of symptoms. It makes good sense to encourage these patients to stay below their critical weight. Interestingly, even patients of normal weight may develop reflux symptoms when they gain weight but do not become overweight or obese. Additionally, patients on low-level treatment may benefit from intermittent medication for symptoms. The medication could be antacids if short-term (about 30 minutes) relief is required, or an H₂-receptor antagonist or proton pump inhibitor if relief for several hours is required.

**Doctor-directed treatment**

When patients present to a physician, they often have tried the above manoeuvres. In some, it may be reasonable to simply emphasise the above and see if they can manage their symptoms on their own. On the other hand, most patients will be treated with a prescription medication.

The end point of therapy should be complete or near-complete resolution of symptoms. H₂-receptor antagonists have an onset of action that is rapid, but rate of symptom relief is about 50% when standard doses are taken twice daily. There is no evidence that greater than standard doses provide additional benefit. Proton pump inhibitors taken once daily provide a higher rate of symptom relief (60–80%) and endoscopic healing (80–90%), but have a somewhat slower onset of action. Once symptom relief is achieved an attempt to step down the dose or change to an ‘as needed’ approach is reasonable. If the patients relapse at that point, they are likely to need long-term treatment. While a prokinetic would seem to be a rational approach to GORD, there are no available, safe and effective agents in this category, leaving acid suppression as essentially the only medical therapy for GORD.

Some patients will have symptoms and/or oesophagitis that do not respond to standard doses of proton pump inhibitors. A common approach is to increase the dose to twice daily (before meals) for an additional 4–8 weeks to see if the disease is brought under control. This approach has not been tested in well-designed trials and it is not clear what proportion of patients will respond. An additional nocturnal dose of H₂-receptor antagonists may be of assistance, but benefits often wear off if given continuously. An alternative is to study the patient using ambulatory reflux testing to either confirm control of acid (on therapy testing) or to determine if they actually have the disease (off-therapy testing or perhaps combined impedance/pH testing). The addition of a prokinetic agent is an attractive concept, but none of the currently available agents have been proven to be effective as either mono or ‘add-on’ therapy in this situation. There are several agents in development that may inhibit transient LES relaxation. Some of the possibilities to be considered when a patient is ‘failing’ proton pump inhibitor therapy are outlined in Table 1.3.

Patients for whom medical therapy results in incomplete resolution of symptoms (especially regurgitation) can achieve that end point with antireflux surgery. Nevertheless, the majority of patients presenting for surgery present because they are keen to achieve long-term cure, without

<table>
<thead>
<tr>
<th>Table 1.3</th>
<th>Failure of proton pump inhibitor therapy to control gastro-oesophageal reflux symptoms: management approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism to consider</td>
<td>Management</td>
</tr>
<tr>
<td>Misdiagnosis</td>
<td>Review history and investigations.</td>
</tr>
<tr>
<td>Not taken before meals</td>
<td>Advise taking 30 minutes prior to a meal.</td>
</tr>
<tr>
<td>Inadequate dosing</td>
<td>Trial twice-daily therapy.</td>
</tr>
<tr>
<td>Nocturnal acid breakthrough</td>
<td>Twice-daily proton pump inhibitor; if that fails, H₂-receptor antagonist before bed as needed; consider surgery.</td>
</tr>
<tr>
<td>Acid hypersecretion</td>
<td>Exclude Zollinger-Ellison syndrome.</td>
</tr>
<tr>
<td>Drug resistance</td>
<td>Very rare; switch to H₂-receptor antagonist or consider surgery.</td>
</tr>
<tr>
<td>Oesophageal hypersensitivity</td>
<td>Add a low-dose tricyclic antidepressant.</td>
</tr>
</tbody>
</table>
Heartburn, regurgitation and non-cardiac chest pain

need for continuing medical therapy and follow-up. Most report the loss of reflux symptoms without the need to take medication from the day of surgery. There is complete control in up to 90% of patients with typical symptoms that responded to acid suppression in the hands of an experienced surgeon. However, in some studies up to 50% of cases eventually will have reintroduction of acid suppression therapy over the long term. The risk of postoperative sequelae has limited the more widespread utilisation of antireflux surgery. The more troublesome of these are painful abdominal distension (gas bloat), persistent dysphagia and, less commonly, persistent diarrhoea.

The surgical approach for most will be laparoscopic. This conveys the advantages of less postoperative pain and early return to full activity. The procedure involves an initial restoration of normal anatomical relationships by reduction of the commonly associated sliding hiatus hernia (see Fig 1.3A) and then wrapping of the lower oesophageal sphincter region with the gastric fundus (see Fig 1.3B). There is still debate as to whether the fundoplication should be complete as shown in Figure 1.3B, or whether the wrap should be incomplete—surrounding less than the 360° circumference of the lower oesophageal sphincter. Current data suggest that patients having the so-called incomplete fundoplication are more satisfied with the outcome because of an apparent reduction in sequelae, even though the long-term control of reflux might not be quite as good as with complete fundoplication. Endoscopic therapies to treat gastro-oesophageal reflux, including radiofrequency therapy, injection of biopolymer and endoscopic sewing around the lower oesophageal sphincter, have been studied. Of these, the systems that place sutures to form a ‘plication’ at the LOS are the only currently available options, while most of the others

Figure 1.3A  Schematic representation of a sliding hiatus hernia (left) and a paraoesophageal hernia (right).

Figure 1.3B  Schematic representation of the Nissen fundoplication operation. From Smout AJPM, Akkermans LMA. Normal and disturbed motility of the gastrointestinal tract. Petersfield: Wrightson Biomedical Publishing; 1972, with permission.
have been removed because of lack of efficacy, unacceptable side effects or both.

**Maintenance therapy**

Once a patient’s symptoms are controlled, they can be entered into a program of ‘maintenance’ in order to keep those symptoms under control. Some patients can be ‘stepped down’ to less complete acid suppression (from high dose proton pump inhibitor to standard dose or from standard dose proton pump inhibitor to H2-receptor antagonist or antacid therapy) and a few can discontinue treatment altogether, especially if they adhere to lifestyle changes. On the other hand, many patients require the same therapy that they needed to achieve remission in order to maintain that remission.

**Risks of long-term acid suppression**

When they were first introduced, the use of proton pump inhibitors was limited to a short period of time. Subsequently, concerns over the potential adverse effects of proton pump inhibitor-induced hypergastrinaemia were discounted and long-term therapy was approved. Acid suppressants have been very safe, but recently a few concerns have arisen. In addition to aiding digestion, gastric acid helps to eliminate ingested bacteria. Infections that have a small increased incidence in proton pump inhibitor-treated patients include *Clostridium difficile*, community-acquired pneumonia and perhaps traveller’s diarrhoea. Acid aids in the absorption of several nutrients (iron, calcium and vitamin B12), although clinically significant insufficiencies are very rare. Recent studies have found a very small increase in hip fractures in proton pump inhibitor-treated patients. Finally, there is no direct cardiovascular risk with acid suppression, although a negative interaction between proton pump inhibitors and the antiplatelet drug clopidogrel has been suggested.

**Clinical management of dysphagia associated with reflux symptoms**

Dysphagia is a ‘warning’ symptom (‘red flag’) in the patient with reflux and must be respected as such. The possibilities include:

- a benign distal oesophageal stricture secondary to GORD;
- a malign out stricture in a patient with GORD;
- dysphagia due to another problem not related to reflux (misdiagnosed achalasia or eosinophilic oesophagitis, for example).

It is often helpful to define the presence and site of stenosis radiologically. Subsequently, the presence or absence of an oesophageal malignancy must be established or disproved by upper gastrointestinal endoscopy and biopsy of the stenosis and any mucosal irregularity. Once malignancy is excluded, oesophageal dilatation may be performed to relieve dysphagia. The dilatation may need to be staged if the stenosis is very narrow and additional care must be taken if the oesophagus has the typical ringed appearance associated with eosinophilic esophagitis. Assuming the patient has symptoms or endoscopy suggestive of GORD, they should start a proton pump inhibitor to achieve symptom control and healing. With this therapy, restenosis is less common. Antireflux surgery should be considered for those who require repeated dilatations or have poor control of heartburn and regurgitation. These patients are sometimes unsuitable for a laparoscopic operation, as oesophageal fibrosis may render the oesophagus short as well as narrow. Some surgeons will perform a Collis gastroplasty (oesophageal lengthening procedure) combined with a Nissen fundoplication in that situation.

Patients with oesophageal involvement from scleroderma are usually readily identifiable by the characteristic appearance of their hands and face. These patients have a hypomotile oesophageal body in addition to a failure of the lower oesophageal sphincter. Aggressive high-level medical therapy is to be preferred over surgical therapy. Oesophageal dysmotility is not isolated to scleroderma and may occur with many other rheumatologic and non-rheumatological conditions (long-standing diabetes, for example).

**Hiatus hernia**

A hiatus hernia is a protrusion of intraabdominal contents through the oesophageal hiatus in the diaphragm. Two main types of hiatus hernia are recognised radiologically (see Fig 1.3A).

**Routine (sliding or fixed) hiatus hernia**

This type of hernia is extremely common (in 10–15% of the population) and often asymptomatic. Its prevalence increases with age. It occurs as a result of circumferential telescoping of the segment of stomach that lies just distal to the lower oesophageal sphincter through the oesophageal hiatus. This type of hernia is not...
prone to obstruction or strangulation, so specific surgical treatment of the hernia is not required; when it is found incidentally in association with GORD, attention should be directed at treatment of the reflux disease. Herniae are more common in more severe grades of esophagitis and are almost universally present in patients with Barrett’s oesophagus.

Paraesophageal (rolling) hernia

This type of hernia is less common. It can range in size from just a small knuckle of fundus protruding alongside the non-displaced lower oesophageal sphincter to the whole stomach twisted and rotated within the posterior mediastinum. With larger herniae, there is a tendency for the lower oesophageal sphincter to be displaced proximally with the stomach. Such herniae should not be thought of as mixed herniae as the main component is usually the paraesophageal component. These herniae can cause dysphagia and uncommonly retrosternal pain due to ischaemia of the entrapped portion of stomach. There may be associated vomiting due to obstruction at either the lower oesophagus or at the gastric outlet. Early satiety and weight loss form part of a milder obstructive syndrome. Large herniae can cause dyspnoea by occupying part of the thoracic cavity, which would otherwise be available for expansion of the lungs. The only effective treatment is surgical repair of the hernia, but this is currently recommended only for patients with symptoms or complications from the hernia. There seems to be a higher than expected recurrence of herniae after repair of the paraesophageal type.

Barrett’s oesophagus

One of the consequences of long-term gastro-oesophageal reflux is a metaplastic transformation of the stratified squamous epithelium of the distal oesophagus to a columnar type epithelium. The affected oesophagus is termed Barrett’s or columnar-lined oesophagus. The significance of Barrett’s oesophagus is its predisposition to malignant change. Clinically, much effort is expended to identify and treat such patients before they present clinically with an adenocarcinoma of the distal oesophagus (Fig 1.4), when the outlook is likely to be poor (Ch 17). It has been suggested that patients with the following characteristics are at greatest risk of developing Barrett’s oesophagus and subsequently oesophageal adenocarcinoma: long-term reflux symptoms, male sex, Caucasian race and positive family history. Despite that, some patients will have reflux symptoms that are so minor that an endoscopy is not likely to be performed on clinical grounds. As a consequence, many patients remain unaware that they carry this malignant predisposition and present at a more advanced stage.

The columnar lining of Barrett’s oesophagus is salmon pink in colour and has a matt surface texture, distinguishing it from stratified squamous epithelium, which is pearly pink in colour and shiny in texture. Histological confirmation is necessary and specialised intestinal metaplasia in the oesophagus is the hallmark finding.

Development of adenocarcinoma in Barrett’s oesophagus is a staged process that occurs over several years. The precursors of invasive carcinoma (low-grade and high-grade dysplasia) can be detected reliably only by histological examination of multiple samples of the columnar epithelium. There are no reliable serological markers or even endoscopic appearances, although advances in endoscopic imaging may change that in the next few years. There is no evidence that control of continuing reflux, after the metaplastic epithelial change has occurred, stops progression down the dysplastic pathway, even though this is appropriate
for control of reflux symptoms. Preliminary data suggest that aspirin may slow the progression of Barrett’s oesophagus to dysplasia and is safe when combined with a proton pump inhibitor.

The aim of the management strategy of patients with Barrett’s oesophagus is to identify patients with high-grade dysplasia. These patients are very likely to proceed in the near future to invasive adenocarcinoma. In patients with non-dysplastic Barrett’s, it is recommended that endoscopic surveillance be conducted every 2–3 years, with biopsies (in each quadrant at 2-cm intervals) along the length of the Barrett’s mucosa. If low-grade dysplasia is identified, the interval should be shortened to at least yearly with a more intensive biopsy pattern (each quadrant every 1 cm). If high-grade dysplasia is found and confirmed, there is a high risk of underlying adenocarcinoma and removal of the Barrett’s epithelium is generally recommended. The traditional approach has been surgical resection of the oesophagus. If performed, as much of the oesophagus as possible should be removed to prevent recurrence of Barrett’s in the residual segment. Recently, endoscopic ablative techniques have been developed and are becoming a recognised alternative in patients with dysplastic Barrett’s epithelium.

Non-cardiac Chest Pain

Non-cardiac chest pain is a diagnosis reached by excluding myocardial ischaemia as the cause of pain by a combination of history taking, physical examination and one or more investigations. Historically, cardiac pain due to ischaemia is primarily retrosternal in position. It may radiate to the neck and jaw, and/or down one or both arms. It is pain that is severe in intensity, crushing in nature and usually not prolonged in duration. It is commonly precipitated by exercise and causes the patient to stop exercising. Patients with cardiac pain are more likely to have evidence of arterial disease in the lower limbs and cerebral arteries, and cardiac risk factors such as hypertension, diabetes mellitus, obesity, hypercholesterolaemia and tobacco use. Severe retrosternal chest pain that radiates through to the back should lead to consideration of dissection of a thoracic aortic aneurysm.

Chest pain of oesophageal origin is more likely to be prolonged, to radiate through to the back, to be precipitated by eating, and to be associated with dysphagia, heartburn and regurgitation. In spite of these differences, chest pain of oesophageal origin cannot be distinguished from cardiac chest pain with any degree of certainty on the basis of history alone. Further, physical examination is rarely of any significant help in separating the two. Signs of heart disease such as cardiac murmurs and cardiac failure, or manifestations of peripheral vascular disease such as bruises and absent pulses, increase the likelihood that the pain is cardiac in origin.

When there is any doubt investigation is initially focused on the heart. All patients should have an electrocardiogram (ECG) and cardiac enzymes measured if they are examined while they are having pain. Those without pain at the time of interview and normal resting ECG should have an exercise stress ECG performed. The extent of further cardiac investigation will depend on clinical judgment. This might include echocardiography, radionuclide studies and coronary angiography. Although coronary angiography remains the gold standard, its performance is sometimes delayed because of its invasive nature and slight risk of complications. The inconvenience and risk obviously need to be weighed against the likelihood that coronary disease will be uncovered and the likelihood that the findings will change the clinical management. One of the advantages of performing coronary angiography that reveals normal coronary arteries is that both patient and doctor can be reassured that sudden death becomes very much less likely. Once the patient is determined to not have occlusive disease of the coronary arteries, several other conditions (below) need to be considered.

Microvascular angina

Microvascular angina is a cause of ischaemic chest pain in the presence of normal coronary arteries; abnormalities may be found on non-invasive cardiac function testing (e.g. radionuclide ventriculography or thallium exercise scintigraphy). It appears these patients have survival rates similar to controls and the pain will, at times, respond to nitrates and/or calcium channel blockers.

Musculoskeletal conditions

Early in the clinical evaluation, before invasive cardiac investigations are performed, the possibility that the chest pain is musculoskeletal in origin should be considered. A history of chest wall injury might indicate a sternal fracture. Palpation of the anterior chest wall may reveal focal tenderness suggestive of costochondritis.

Panic attacks

Panic attacks can cause chest pain. They result in discrete periods of intense fear that occur abruptly with at least four of the following...
symptoms: chest pain, palpitations, sweating, trembling, shortness of breath, choking, nausea, dizziness, feelings of unreality or detachment, fear of losing control, fear of dying, paraesthesia and flushes or chills.

**Oesophageal conditions**

Oesophageal conditions that can cause non-cardiac chest pain, in order of importance, include:

- GORD (most common);
- non-specific motility disorder or hypertensive lower oesophageal sphincter (uncertain significance);
- high pressure ‘nutcracker’ oesophagus (uncertain significance);
- diffuse oesophageal spasm (rare); and
- achalasia (rare).

These conditions can be diagnosed either by endoscopy and pH monitoring in the case of GORD, and by oesophageal manometry in the remainder. Unfortunately it is often difficult to be sure that the oesophageal condition diagnosed is indeed the cause of the pain, as will be discussed below.

The program of investigation for patients deemed to have non-cardiac chest pain that might be oesophageal in origin will depend on how significant the symptoms are in terms of both their severity and frequency. Some patients will do well if reassured that their heart is not the cause of their symptoms. GORD should be the first consideration for the aetiology of oesophageal pain. If the patient has co-existing heartburn or regurgitation, a reflux aetiology is more likely. The diagnostic option is to either perform an ambulatory reflux test or offer a trial of proton pump inhibitor (PPI). The so called ‘PPI-test’ is a short-term (7–14 day) trial of a twice daily proton pump inhibitor that seems to have a reasonable sensitivity and specificity when compared to ambulatory pH testing. An ambulatory reflux test should be considered ‘positive’ if there is excess reflux or if symptoms occur in correlation with episodes of reflux. If proton pump inhibitor treatment is effective, it should obviously continue. The role of endoscopy in patients without typical symptoms in unclear, but the finding of erosive oesophagitis may clinch the diagnosis.

If the patient fails a treatment trial or if the symptoms are clearly related to swallowing, an oesophageal motility test may be of benefit although the minority of patients will have a clearly definable motility disturbance. The manometric characteristics of motor disorders that may cause non-cardiac chest pain are shown in Table 1.4. Unfortunately, manometry has significant limitations in this clinical setting as it is performed in a laboratory over a short time frame (which is standard) and the chance that the abnormal manometric findings will be observed, except in the case of achalasia, is low. This likelihood can be increased by using provocative agents, such as edrophonium, or extending the period of observation utilising a portable ambulatory manometry system. Effective therapy for diffuse oesophageal spasm, nutcracker oesophagus, non-specific motility

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Achalasia (see Ch 2)</td>
<td>● Incomplete relaxation of the lower oesophageal sphincter</td>
</tr>
<tr>
<td></td>
<td>● Aperistalsis of the oesophageal body</td>
</tr>
<tr>
<td>Diffuse oesophageal spasm</td>
<td>● Simultaneous contractions (&gt; 10%)</td>
</tr>
<tr>
<td></td>
<td>● High-amplitude contractions (&gt; 180 mmHg)</td>
</tr>
<tr>
<td></td>
<td>● Repetitive synchronous oesophageal body contractions (&gt; 2 peaks)</td>
</tr>
<tr>
<td></td>
<td>● Prolonged oesophageal body contractions (&gt; 6 s)</td>
</tr>
<tr>
<td>Nutcracker oesophagus</td>
<td>● High-amplitude peristaltic contractions (&gt; 180 mmHg)</td>
</tr>
<tr>
<td></td>
<td>● Prolonged oesophageal body contractions (&gt; 6 s)</td>
</tr>
<tr>
<td>Hypertensive lower oesophageal sphincter</td>
<td>Elevated lower oesophageal sphincter pressure (&gt; 45 mmHg)</td>
</tr>
<tr>
<td>Non-specific motility disorder</td>
<td>One or more of the following:</td>
</tr>
<tr>
<td></td>
<td>● non-transmitted contractions (&gt; 20%);</td>
</tr>
<tr>
<td></td>
<td>● repetitive oesophageal body contractions (&gt; 2 peaks);</td>
</tr>
<tr>
<td></td>
<td>● prolonged oesophageal body contractions (&gt; 6 s);</td>
</tr>
<tr>
<td></td>
<td>● low-amplitude peristalsis (&lt; 30 mmHg);</td>
</tr>
<tr>
<td></td>
<td>● frequent spontaneous contractions.</td>
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</tbody>
</table>
disorder and hypertensive lower oesophageal sphincter is currently not available. Therapeutic trials of nitrates or a calcium channel blocker are worthwhile, but should be discontinued if there is no apparent response.

A group of patients will remain for whom no diagnosis will be achieved after all investigations have been completed and therapeutic trials undertaken. These patients probably have visceral hypersensitivity, a variant of irritable bowel syndrome. For the sufferer of chest pain, there is likely to be a significant degree of anxiety because of the fear of possible sudden death. Clearly, these patients need to be reassured sympathetically that it is very unlikely that their condition, although distressing, will be progressive or fatal and that continued observation is quite appropriate. Some of these patients will benefit from antidepressant therapy (e.g. low-dose tricyclic antidepressant).

**Key Points**

- Heartburn, regurgitation or both are the cardinal symptoms of gastro-oesophageal reflux disease (GORD).
- Other GORD-related symptoms may include choking attacks, cough, asthma, hoarseness of voice, a foul taste in the mouth in the morning, bad breath, a sore tongue, dental caries and nasal aspiration.
- Dysphagia related to reflux is usually caused by a benign stricture, but endoscopy is required to rule out malignant causes and also allows dilation of any stricture.
- Endoscopy is required in GORD patients with alarm features such as vomiting, bleeding, weight loss or dysphagia. Patients with long-standing symptoms are at risk for Barrett’s oesophagus and should also undergo endoscopy.
- Ambulatory reflux testing is used to confirm or refute reflux in difficult cases, particularly when surgery is being considered.
- The combination of lifestyle changes and medical therapy (usually with a once-daily proton pump inhibitor) will control GORD in the vast majority of patients.
- Barrett’s oesophagus is a consequence of GORD and places patients at an increased risk of developing adenocarcinoma of the oesophagus.

Fortunately, most patients with Barrett’s oesophagus do not progress and patients in surveillance programs for Barrett’s oesophagus usually progress slowly allowing for effective intervention using endoscopic or surgical approaches.

- The oesophagus may be the cause of chest pain similar to angina.
- Cardiac causes should be carefully excluded in any patient with chest pain prior to considering an oesophageal origin.
- Reflux is the most common cause of non-cardiac chest pain, with some other patients suffering from spastic oesophageal motility disorders such as nutcracker oesophagus or diffuse oesophageal spasm.

**Further reading**


