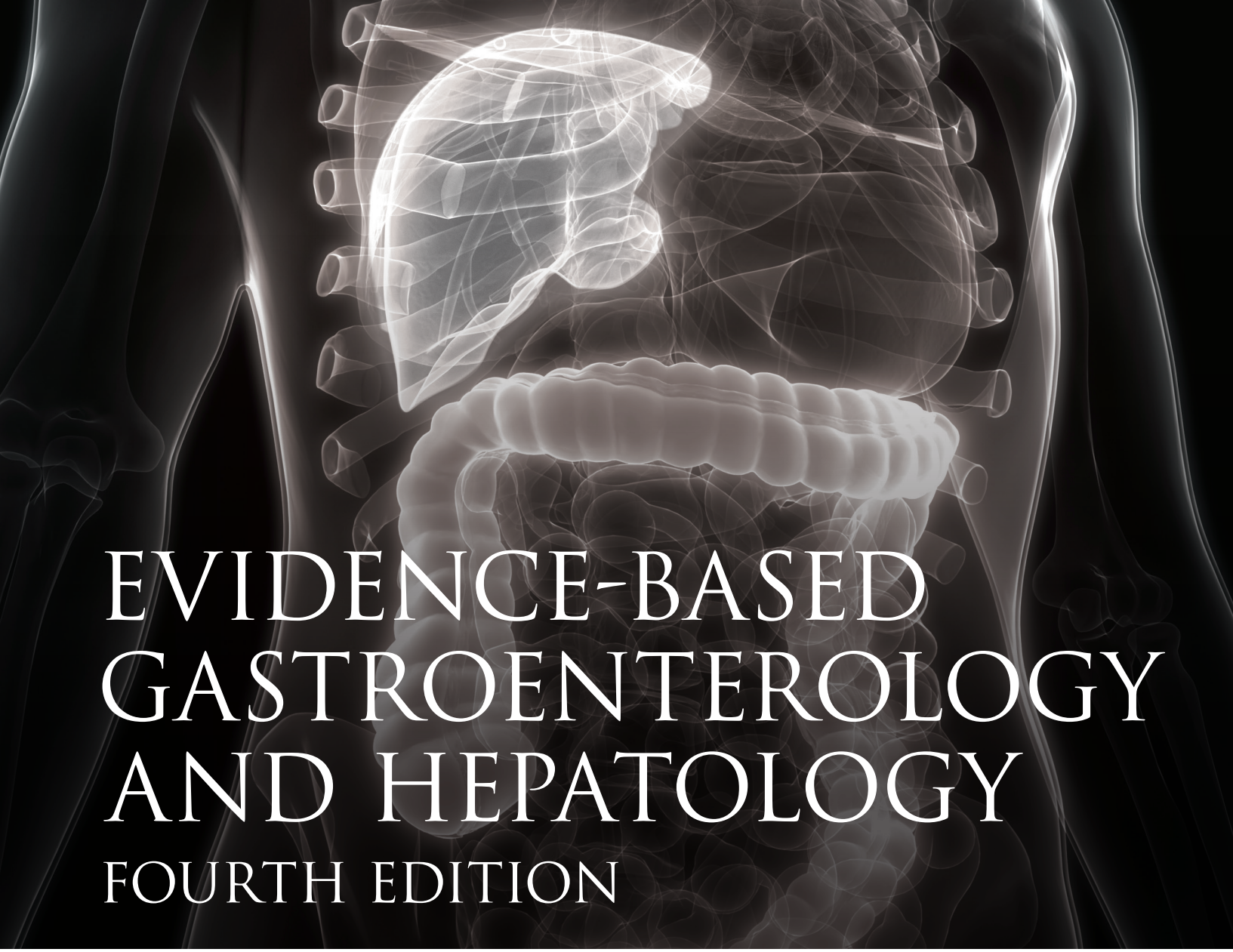

EVIDENCE-BASED GASTROENTEROLOGY AND HEPATOLOGY

FOURTH EDITION

Edited by
John W. D. McDonald
Brian G. Feagan
Rajiv Jalan
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WILEY Blackwell

Evidence-Based Gastroenterology and Hepatology

Fourth Edition

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Dedication

We dedicate this edition to the authors Dr. David Sackett and Professor Andrew Burroughs.

David Sackett

Dr. **David Sackett**, in his final year as a medical student, David "Dave" Sackett was involved in the care of a young patient with acute viral hepatitis, who was being managed with the conventional treatment of enforced bedrest. Dave read a small, simple randomized trial of bedrest for this disease and realized that there was no evidence for this approach. He was always brave and sometimes unconventional, and he released the young man from bedrest, defying convention in favor of evidence. This started his 60-year career in promoting the approach for which he initially coined the term "critical appraisal" and which one of his students, Dr. G. Guyatt, eventually named "evidence-based medicine." He promoted this approach very strongly from his primary academic base at McMaster University, but also from his career from 1994 to 1996 at the University of Oxford, where he established the International Centre for Evidence-Based Medicine and served as the first Chair of the Cochrane Collaboration. It was during his time at Oxford, and in collaboration with BMJ Books, that he strongly promoted the creation of several evidence-based medical textbooks, including this one, of which the first edition was published in 1997.

Born in Chicago, Dr. Sackett became a Canadian citizen after his move to McMaster University in 1974. In his long and distinguished career, Dr. Sackett accepted many prestigious awards, but was most proud of being named an officer of the Order of Canada, an award that in his view recognized his contribution to the larger community, not just to medicine. He was a direct participant and leader in the design and execution of many important randomized trials; however, one of his greatest legacies is the work of the 300 young students and clinical scientists whom he mentored in their learning of evidence-based approaches to care. Many of these students, including such leaders as Dr. Brian Haynes and Dr. Gordon Guyatt, learned from Dave when he served at his academic base at McMaster University and its hospitals. A great many young people benefited from his approach when with his wife Barbara and he hosted them at his rural and rustic "retirement" site, which he named the Trout Research & Education Centre.

"Dave" died of metastatic cholangiocarcinoma in 2015.

Andrew Burroughs

Andrew Burroughs was instrumental in bringing and implementing the practice of modern hepatology to the great Royal Free Hospital that was started by late Dame Sheila Sherlock, who was Andy's proud mentor, and afterwards by Prof Neil McIntyre. His contributions to hepatology are innumerable but his research made a real difference to the understanding and clinical management of portal hypertension, primary biliary cirrhosis, hepatocellular carcinoma, and liver transplantation. His H-index is well over a 100 and he has over 600 peer-reviewed publications. He mentored over 100 fellows from around the world, most of whom are now leaders in the field. He provided leadership to British and European hepatology by getting involved in policy and advocacy at every level.

Andy was an excellent example of a true blue clinical-academic; a great physician, a dedicated and inspiring teacher, a questioning researcher, and a true leader in the field of hepatology.

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Preface

Over the past four decades the emergence of evidence-based medicine (EBM) has had a substantial impact on clinical practice. In the first half of the twentieth century, diagnostic tests or treatments, usually based on a strong scientific rationale and experimental work in animals, were routinely introduced into clinical care without good scientific proof of efficacy in people. Some of these interventions, such as gastric freezing for the treatment of ulcers and penicillamine therapy for primary biliary cirrhosis, were ultimately shown to be ineffective and harmful [1, 2]. Fortunately, the need for a more critical approach to medical practice was recognized. In 1948, the first randomized controlled trial (RCT) in humans was carried out under the direction of the British Medical Research Council [3]. Epidemiologists and statisticians, notably Sir Richard Doll and Sir Bradford Hill, provided scientific leadership to the medical community, which responded with improvements in the quality of clinical research. The use of randomized allocation *to control for confounding variables and to minimize bias* was recognized as invaluable for conducting valid studies of treatments. The RCT soon became the benchmark for the evaluation of medical and surgical interventions. In 1955, Professor Sidney Truelove conducted the first randomized trial in the discipline of gastroenterology [4], proving that cortisone was more effective than a placebo for the treatment of ulcerative colitis.

Gastroenterologists, hepatologists, and general surgeons are fortunate to have many excellent textbooks that provide a wealth of information regarding digestive diseases. Many traditional textbooks concentrate on the pathophysiology of disease and are comprehensive in their scope. *Evidence-Based Gastroenterology and Hepatology* is not intended to replace these texts, since *its focus is on clinical evidence*. Excellent electronic databases are available, and many traditional publications contain relevant research evidence and important summaries and reviews to support evidence-based practice. However, physicians in clinical practice find that locating relevant articles and analyzing relevant data from these sources is very time consuming. This book has been written for the purpose of saving valuable time for busy practitioners of gastroenterology and hepatology, and for general internists and general surgeons who deal with substantial numbers of patients with disorders ranging from gastroesophageal reflux disease to liver transplantation. Authors have endeavored to provide the most recent evidence as the basis for recommendations.

The introduction to the third edition of this book presented detailed examples of the analysis of evidence for decision-making regarding causation, diagnosis, prognosis, and therapy. This chapter has been made available online at https://media.wiley.com/product_data/excerpt/31/14051819/1405181931.pdf and can be accessed by students and practitioners who would like to review this detailed and comprehensive discussion. However, the principles of EBM are now widely taught and accepted, reducing the need for this kind of detail in the introductory chapter. Instead, we wish to use this space to recognize the extremely important contributions made by two physicians to the development of this book, both of whom have died since the last edition was published, Dr. David Sackett and Professor Andrew Burroughs.

PART I

Gastrointestinal disorders

1 CHAPTER 1
Gastroesophageal reflux disease

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Introduction

Gastroesophageal reflux disease (GERD) is a "condition that develops when the reflux of stomach contents causes troublesome symptoms and/or complications" [1]. It is frequently encountered in clinical practice; in 2004, GERD accounted for about 18 million ambulatory care visits or 17% of all digestive disease encounters in the United States of America [2]. Although a variety of symptoms might be associated with GERD, none are pathognomonic. However, in cases presenting with the typical GERD symptoms of heartburn and regurgitation and without "alarm symptoms" of bleeding, dysphagia, or weight loss, it is common practice to treat GERD without investigation.

Definition of GERD

Gastroesophageal reflux (GER) is a physiological event that commonly occurs during and after meals. Such physiological reflux episodes are rapidly cleared by esophageal peristalsis and the residual acidity neutralized by the bicarbonate in swallowed saliva. Physiologic GER is generally asymptomatic [3]. GER becomes pathological when reflux episodes are frequent, occur outside of the postprandial period, and induce typical (heartburn, regurgitation) or atypical symptoms (dysphagia, chest pain, cough, etc.) of sufficient magnitude that they become "troublesome" to the individual. It is difficult to precisely demarcate the transition between physiological GER and GERD based on symptom frequency or intensity, but the "troublesome" threshold was adopted to imply a decrement in quality of life [1]. Having some degree of heartburn is considered normal. Moreover, only a small proportion of patients with GERD seek medical care for the condition [4].

According to the Montreal definition, GERD can also be defined by syndromes characterized by esophageal injury, including reflux esophagitis, Barrett's esophagus, peptic stricture, or adenocarcinoma [1]. This umbrella definition was devised to encompass the broad spectrum of GERD inclusive of both erosive reflux disease (endoscopically defined esophagitis and complications thereof), nonerosive reflux disease (NERD) (patients with troublesome esophageal GERD symptoms, but without esophagitis on endoscopy), and patients with extra-esophageal manifestations of GERD such as laryngitis or cough.

Clinical presentation

The typical symptoms of GERD are heartburn (a burning sensation arising behind the breastbone toward the neck) and regurgitation (experienced as refluxed fluid moving in the chest or a bitter taste in the mouth). However, even these typical symptoms are not specific for GERD as demonstrated by the Diamond study, which evaluated the accuracy of the reflux disease questionnaire (RDQ) for the diagnosis of GERD. The RDQ utilizes six items to score the occurrence and frequency of heartburn, regurgitation, and dyspepsia. In a cohort of 308 patients with troublesome upper gastrointestinal symptoms, the sensitivity and specificity of the RDQ to diagnose GERD were 62% and 67%, respectively, when using the findings from endoscopy and wireless pH-metry as the reference standard [5].

Atypical GERD symptoms can be esophageal or extra-esophageal. Dysphagia is experienced by one-third of GERD patients [6]. This "warning sign" should lead to upper GI endoscopy with esophageal biopsies to evaluate for esophagitis, tumor, stricture, and eosinophilic esophagitis. Chest pain may also be attributed to GERD in up to 50% of patients [7]. However, due to the potential life-threatening nature of cardiac disease, a cardiac evaluation should be prioritized in such patients before accepting an esophageal etiology.

GERD is an etiology of chronic cough and estimates of the prevalence of GERD-associated cough range from 0% to 41% of chronic cough cases [8]. Half of asthma patients have evidence of GERD [9]. A variety of ear nose and throat (ENT) symptoms have been attributed to reflux: dysphonia, globus

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sensation (perception of a lump or fullness in the throat, irrespective of swallowing), throat clearing, sore throat, chronic laryngitis, and laryngospasm. However, controversy persists regarding diagnostic criteria for these "laryngopharyngeal reflux" syndromes, especially between gastroenterologists and ENT physicians [10].

Gastrointestinal symptom scales were recently developed using the National Institutes of Health (NIH) Patient-Reported Outcomes Measurement Information System (PROMIS®) [11]. These scales are intended for use in clinical care and research. Items were determined based on literature searches and administered to patients with gastrointestinal conditions and to the general population. The GER domain items assess: (i) sensations associated with food intake (reflux, regurgitation) or not associated with food intake (lump in the throat); (ii) painful sensations (heartburn, chest pain, throat burn); and (iii) belching, gas (burping), and hiccups. Symptoms occurring during the past seven days are scored.

Epidemiology

Since the criteria used to define GERD in epidemiological studies differ from the Montreal definition, it is difficult to know the actual prevalence of GERD in the general population. However, based on self-reporting of at least weekly heartburn and/or regurgitation estimates of the prevalence of GERD range from 9% to 33% (Table 1.1) [12].

The pitfalls of GERD prevalence estimates were well elucidated by the Diamond study, conducted in primary care practices in Europe and Canada [5]. Three hundred and eight patients with upper GI symptoms underwent a systematic evaluation with endoscopy, esophageal pH monitoring, structured interviews, questionnaires, and a trial of proton pump inhibitor (PPI) medication. Among these patients, 38% were found to have esophagitis, 28% had abnormal esophageal pH-metry, and 49% identified heartburn or regurgitation as their most bothersome symptom. Response to two-week PPI treatment did not clarify these discrepancies. Even though a beneficial PPI response was more frequent in patients with esophagitis (69%) and in patients with normal endoscopy and abnormal esophageal pH-metry (49%), 35% of patients with normal examinations also had symptom improvement [13].

Table 1.1 GERD prevalence worldwide

Geographic location	Estimates of GERD prevalence based on self-reporting heartburn and/or regurgitation
USA	18–28%
Europe	9–26%
South America	23%
Middle East	9–33%
East Asia	3–8%
Australia	12%

Source: Adapted from El-Serag *et al.* 2014 [12].

Major risk factors associated with GERD are age, pregnancy, and obesity. The incidence of GERD increases with age [14]. Half to two-thirds of pregnant women report GERD symptoms [15]. In Western countries, the increased prevalence of GERD has occurred in parallel with increased obesity, evident by an increased prevalence in both obese (body-mass index (BMI) > 30 kg/m^2) and overweight (BMI 25–30 kg/m^2) patients [16].

GERD is also associated with other disease entities including diabetes mellitus [17] and pulmonary disease. Chronic pulmonary diseases and asthma were associated with new GERD diagnoses in a study utilizing the UK General Practice Research Database [14]. Impaired esophageal function is encountered in 80% of scleroderma patients and this frequently leads to GERD symptoms [18]. Esophagitis was observed in 42% of patients with Zollinger–Ellison syndrome, which promotes GERD by increasing the acidity and quantity of gastric acid in the refluxate [19].

Pathophysiology

During physiological reflux, gastric content enters the distal esophagus and is then rapidly cleared by peristalsis. Physiological reflux occurs almost entirely by transient lower esophageal sphincter relaxation (TLESR), which is a complex vago-vagal reflex involving non-deglutitive lower esophageal sphincter (LES) relaxation [20], crural diaphragm inhibition, and distal esophageal shortening. TLESRs are triggered by gastric distension with food, liquid or gas and are the physiological mechanism of belching.

Only a fraction of TLESRs are associated with acid reflux and that fraction is greater in GERD patients than in controls [21]. Another differentiating feature of GERD patients is that reflux can occur by mechanisms other than TLESR. This is especially true in patients with hiatus hernia, a situation in which the LES and the crural diaphragm (CD) are spatially separated. Normally, these elements act in concert as the antireflux barrier at the esophagogastric junction (EGJ), but their spatial separation, be that intermittent or constant, facilitates the occurrence of reflux [22]. Hiatus hernia also predisposes to swallow-induced reflux and strain-induced reflux, especially when associated with a hypotensive LES [23]. Yet another impairment associated with hiatus hernia is of prolonged acid clearance as gastric juice within the hernia refluxes back and forth across the LES with swallows while subjects are in a recumbent posture [23]. Not surprising, hiatus hernia is observed in up to 70% of patients with esophagitis, more so with increasing severity of the esophagitis [24]. Finally, hiatus hernia interacts with the acid pocket, the newly secreted acid that layers on the top of

gastric content in the postprandial period, serving as the reservoir for postprandial acid reflux. With hiatus hernia, the acid pocket is displaced proximally into the hernia compartment, greatly facilitating its access to the distal esophageal mucosa [25].

Although the dominant mechanism of prolonged acid clearance, and consequently prolonged esophageal acid exposure time, in GERD patients is hiatus hernia, clearance is also compromised by weak, or even absent, peristalsis [26]. Peristalsis, primary or secondary, clears the refluxed fluid back to the stomach and ineffective esophageal motility is associated with impaired esophageal clearance [27]. The final step in acid clearance after a reflux event is neutralization of residual acid by swallowed saliva [28]. Hence, hyposalivation, as occurs with many medications, certain collagen vascular diseases, and during sleep can prolong the process of acid clearance and thereby exacerbate the severity of GERD [29, 30].

There is also interplay between the efficacy of gastric emptying and GERD, which is a frequent accompaniment of gastroparesis. However, the relationship is less clear with marginal abnormalities of gastric emptying. In a series of 30 patients referred for both a gastric emptying study and esophageal pH-impedance monitoring, delayed gastric emptying was associated with an increased number of postprandial reflux episodes, but no significant difference in acid esophageal exposure [31]. On the other hand, accelerating gastric emptying with the 5-HT4 receptor agonist prucalopride reportedly decreased esophageal exposure time, but had no effect on the number of reflux episodes in 21 healthy controls [32].

Although the severity of esophagitis correlates with the extent of esophageal acid exposure as determined by pH monitoring studies, the same relationship does not hold for reflux symptom severity. Only 20–40% of patients with GERD symptoms have erosive reflux disease defined by esophageal mucosal breaks [33, 34] and pathological reflux on esophageal pH-metry is reportedly found in only 21–61% of NERD patients [35, 36]. Hence, the determinants of symptom severity are somewhat distinct from those of mucosal erosion. Mucosal injury is facilitated by prolonged exposure to refluxed acid, pepsin, and bile acids. Symptoms, on the other hand, are strongly modulated by sensitivity. Only about 10% of reflux episodes are symptomatic [37], and patients with pathological GERD are more sensitive to acid and esophageal distension than are control subjects [38]. Reflux episodes during which the refluxate reaches the proximal esophagus, which are more common among GERD patients, are also more likely to be symptomatic, and recent physiological data suggest that the proximal esophagus is more sensitive to reflux than is the distal esophagus [39]. Finally, the phenomena of hypersensitivity and hypervigilance are increasingly recognized as major determinants of symptom severity among subsets of NERD patients [40].

Natural history and complications

GERD can present as erosive reflux disease with esophageal mucosal breaks on endoscopy or as NERD, in which case there are symptoms attributable to GERD without endoscopically evident disease. NERD is the dominant form, encountered in about 70% overall [41]. Potential complications of GERD include bleeding, esophageal stricture, Barrett's esophagus, and esophageal adenocarcinoma. Barrett's esophagus is defined as the replacement of normal squamous esophageal mucosa with columnar epithelium found to contain intestinal metaplasia on histopathology. Barrett's esophagus is the major risk factor for the development of esophageal adenocarcinoma (see Chapter 2).

Only a few studies have examined the natural history of GERD. Both progression from NERD and regression from erosive disease have been observed. Illustrative of this are data from a large multicenter study of 6215 patients conducted in Germany, Austria, and Switzerland reporting progression, regression and stability of GERD within that population [42]. Among 2721 patients who completed the five-year follow up, most remained stable or improved with routine clinical care. Among patients with severe esophagitis at baseline, 61% had NERD at five years. On the other hand, disease progression was observed in 6% of NERD patients, 12% of patients with grade A/B esophagitis, and 19% of patients with grade C/D. In a recent comprehensive review, Savarino reported progression from NERD to erosive disease in 0–30% of patients, progression from mild to severe esophagitis in 10–22%, and progression from erosive disease to Barrett's esophagus in 1–13% [41].

While GERD does not decrease life expectancy [14], it does impair quality of life. In the Kalixanda study, daily symptoms were associated with a greater decrement in quality of life than were less frequent symptoms [43]. Interestingly, esophagitis did not significantly alter quality of life in that study. GERD is also responsible for absenteeism and up to 30% of patients with heartburn reported reduced productivity at work, especially those with nocturnal symptoms [44].

Diagnostic tests

GERD is usually a clinical diagnosis based on a symptom assessment. Testing is reserved for cases in which there are warning signs of complication, atypical symptoms such that the diagnosis is in doubt, an inadequate response to medical treatment, or as a preoperative evaluation to confirm the diagnosis prior to surgical treatment. Hence, the diagnostic approach utilized varies greatly depending on a symptom assessment, an assessment of the risk that complications exist, the history and success of treatment trials, whether or not a potentially morbid therapy is under consideration, and the history of prior testing. As a general rule, the extent of diagnostic testing pursued should be limited to that which

guides management decisions and/or protects the patient from risk.

Symptom assessment and questionnaires

The occurrence of typical heartburn and/or acid regurgitation in a patient without signs of potential complications (dysphagia, odynophagia, weight loss, bleeding, or anemia) is sufficient to diagnose GERD and initiate therapy. Standardized questionnaires have been developed to aid in the clinical diagnosis of GERD. These were devised to facilitate screening patients for GERD in primary care settings and to provide a standardized evaluation. In a recent review, Bolier *et al*. identified 39 questionnaires to assess GERD symptoms, 14 to assess response to treatment, and 18 to assess GERD-related quality of life [45]. The RDQ is the most widely used, consisting of six items that assess the frequency and severity of heartburn, regurgitation, and dyspepsia. Alternatively, the GerdQ questionnaire includes six items (heartburn and regurgitation frequencies, stomach pain, nausea, nocturnal symptoms, and requirement of additional medication) and was also translated in multiple languages. The accuracy of these questionnaires in diagnosing GERD varies with what is being used as the reference standard. If the comparison is with the diagnoses rendered by an experienced clinician [5], the correspondence is very good; if the comparison is to physiological testing and endoscopy, the sensitivity and specificity are only about 65% [46].

PPI trial

The high prevalence of GERD and the impressive therapeutic efficacy of PPIs led some authors to propose using a PPI trial to diagnose GERD. However, as evident from the findings of the Diamond study, responsiveness to PPI therapy, abnormal pH-metry, and symptom-based assessments each detect unique patient populations, which only partially overlap. Illustrative of this, a positive PPI trial was observed in 69% of patients meeting pH-metry and/or endoscopic criteria of GERD in the Diamond study and in 51% of patients not meeting these criteria [13]. Similar findings were reported in a meta-analysis of 15 studies using many variations of the "PPI test." With 24-hour pH-metry as the reference standard, the positive likelihood ratio of the PPI trial for predicting GERD ranged from only 1.63 to 1.87 [47].

The imperfect overlap between patient populations defined by physiologic testing and response to a PPI trial does not negate the practicality and cost-effectiveness of empiric therapy. Fass *et al*. reported that, although a protocol of omeprazole 60 mg daily had relatively poor test characteristics for detecting physiologically defined GERD (sensitivity 80%, specificity of 57%), this protocol saved an average of US $348 per patient with a 64% reduction in the number of upper GI endoscopies and 53% reduction in the use of pH-monitoring [48]. However, empiric PPI therapy also has its limitations. A positive response may be attributable to a placebo effect or the presence of an alternative acid-peptic disorder, while a negative response may occur in truly PPI-refractory GERD. Other considerations are the potential to mask malignancies and to foster inappropriate long-term PPI use, which has clinical and economic implications. In summary, empiric PPI therapy is a simple and cost-effective way to manage typical reflux symptoms in patients without warning signs, but the effectiveness of the therapy does not equate to a diagnosis of GERD.

Upper GI endoscopy

Upper GI endoscopy is the best test for detecting GERD complications and for excluding alternative diagnoses such as malignancy, eosinophilic esophagitis, or peptic ulcer. With respect to establishing a GERD diagnosis, the minimal endoscopic lesion with acceptable inter-observer agreement (kappa 0.4) is a mucosal break, the basis for the Los Angeles classification. Grades A–D of the LA classification are illustrated in Figure 1.1 [49]. The severity of esophageal acid exposure is significantly related to the LA grade of esophagitis, but it is important to note that mild esophagitis (grade A) was found in 5% of asymptomatic controls [34] leading some to question the significance of this finding. Among 280 075 upper GI endoscopies performed between 2000 and 2005 in the Clinical Outcomes Research Initiative (CORI) database, esophagitis was found in 17.3%, esophageal stricture in 9.5%, and Barrett's esophagus in 4.5% [50]. Esophagitis was graded according to the LA classification in fewer than 50% of endoscopies; when documented, esophagitis was grade A or B in 79% of patients.

Upper GI endoscopy might also be useful to detect hiatus hernia. However, estimates of the prevalence of hiatus hernia in the adult population vary enormously from 10% to 80% [51] likely due to subjectivity of diagnostic criteria. In the CORI database, hiatal hernia was observed in 33% of upper GI endoscopies and in 40–45% of patients undergoing endoscopy for reflux symptoms [50]. Thus, even though relevant to a GERD diagnosis, the presence of hiatal hernia is not sufficient to establish that diagnosis.

Histologic examination of distal esophageal mucosal biopsies might increase the diagnostic yield of endoscopy for GERD. Microscopic esophagitis was observed in 65% of NERD patients, but also 15% of controls [52]. Kandulski *et al*. proposed a histological score combining degree of basal cell hyperplasia, presence of papillary elongation, dilated intercellular spaces and inflammation. A score ≥ 5 had a sensitivity of 85% and a specificity of 64% to differentiate NERD from functional heartburn [53].

In summary, endoscopy is an important test to detect complications of GERD and for excluding alternative diagnoses that might explain a patient's symptoms. However, its sensitivity for diagnosing GERD is poor.

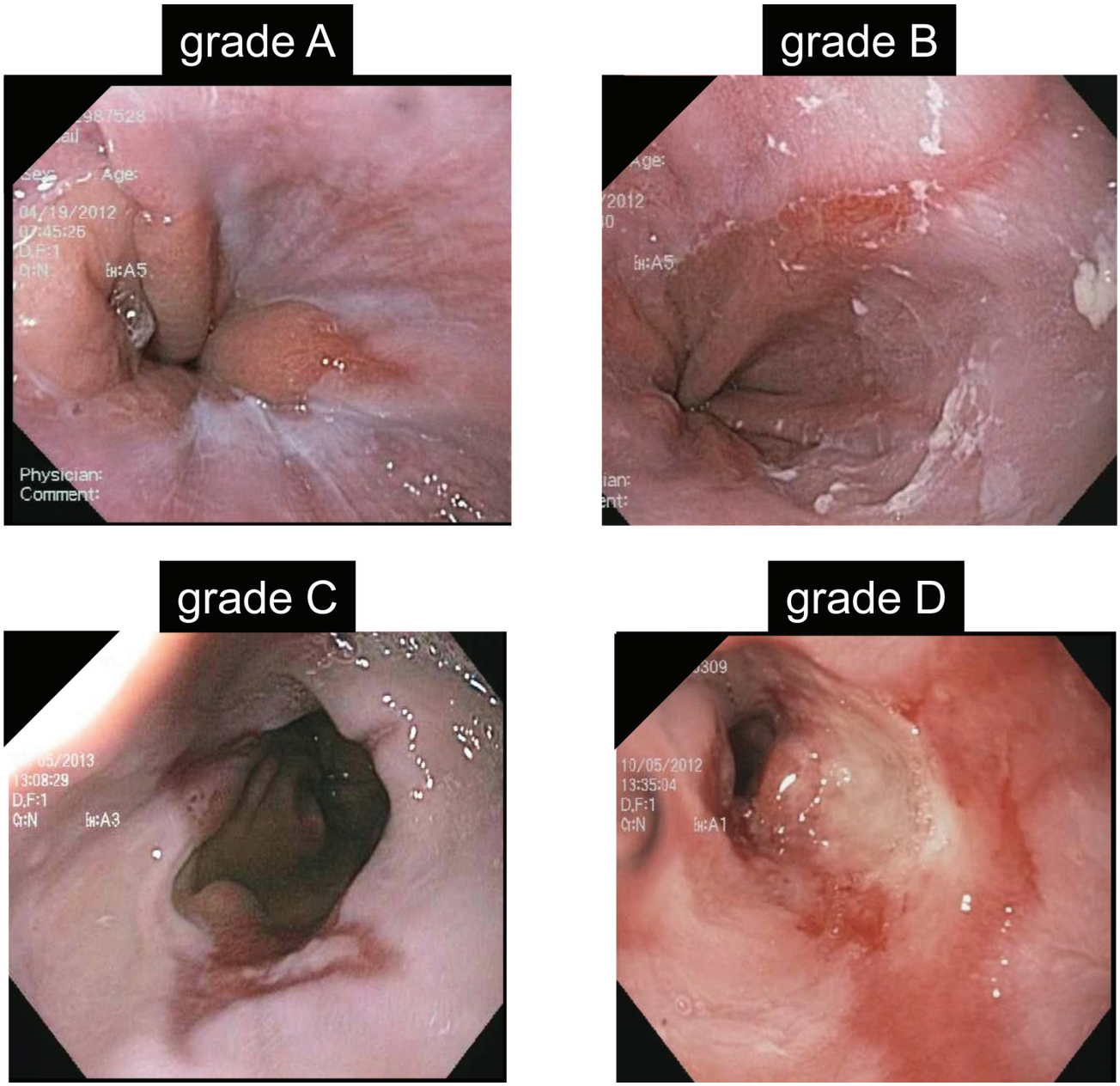

Figure 1.1 Los Angeles Classification. Grade A is defined as one (or more) mucosal break no longer than 5 mm that does not extend between the tops of two mucosal folds. Grade B is defined as one (or more) mucosal break longer than 5 mm that does not extend between the tops of two mucosal folds. Grade C is defined as one (or more) mucosal break that is continuous between the tops of two or more mucosal folds but which involves less than 75% of the circumference. Grade D is defined as one (or more) mucosal break which involves at least 75% of the esophageal circumference.

Ambulatory GERD testing: pH and pH-impedance monitoring

Ambulatory reflux monitoring can detect pathological reflux in patients without endoscopic esophagitis. Conventional (or wireless) pH-metry detects reflux events on the basis of their acidity, while pH-metry combined with impedance detects all liquid and/or gas reflux. Both methods can be used to correlate reflux events with patient-reported symptoms, albeit in the case of pH-metry this analysis is restricted to acid reflux events.

Ambulatory pH-metry studies are done positioning the pH electrode 5 cm above the proximal margin of the LES or, in

the case of wireless monitoring, 6 cm above the squamocolumnar junction. Esophageal acid exposure is defined as the percentage of the recording time with esophageal pH < 4; the threshold that is most discriminative in differentiating physiological and pathological reflux [54]. Reported upper limits of normal for esophageal acid exposure with catheter-based systems range from 3.9% to 7.2% and for the wireless system from 4.4% to 5.3% [55–57]. The sensitivity and specificity of pH-metry for differentiating control subjects from esophagitis patients are 77–100% and 85–100%, respectively [58–61]. Advantages of wireless pH-metry over catheter-based studies are of improved tolerability and studies that can be prolonged for up to 96 hours, thereby improving the yield for detecting abnormal reflux. Illustrative of this, among 38 patients with normal acid exposure on catheter pH-metry, pathological acid exposure was detected in up to 47% of patients using the wireless technology [62].

Compared to pH-metry, pH-impedance monitoring characterizes reflux not only by its acidity, but also by its gas/liquid content, its direction of flow, and the proximal extent to which it flows into the esophagus. These are all factors potentially relevant to symptom perception, especially in patients taking acid suppressive medication [63]. As with catheter-based pH-metry, the pH-impedance probe is passed transnasally into the esophagus and connected to an external receiver. Combined pH-impedance studies are analyzed both for esophageal acid exposure time and for the number of reflux events, acid or otherwise, with the upper limit of normal reported as ranging from 54 to 75 per 24 hours [64, 65]. When the study is performed withholding PPI therapy there is a nominal increased yield relative to pH-metry alone reported to range from 6% to 11%, attributable to weakly acidic reflux events that correlate with reported symptoms [64]. However, the significance of that increased yield is unclear, given that abnormal acid exposure, but not an abnormal number of reflux episodes, correlates with medical or surgical treatment outcome [66].

Both pH-metry and pH-impedance monitoring are also used to test the relationship between reflux events and patient-reported symptoms. The two most popular indices are the symptom index (SI) and the symptom association probability (SAP). The SI is defined as the percentage of symptom events that occur within two minutes of reflux episodes, irrespective of the number of reflux episodes recorded, with a value of >50% considered positive [67]. A high SI can occur by chance, especially in a patient with numerous reflux episodes. To improve upon this, the SAP is a statistical calculation assessing the probability that the reflux and symptoms co-occur by chance; an SAP >95% is considered significant [68]. However, according to the Rome IV criteria for functional esophageal disorders, the finding of a normal esophageal acid exposure and a positive SI or SAP is now considered reflux hypersensitivity rather than GERD [69]. Consequently, although the SI and SAP may be useful to establish a relationship between reflux events and symptoms, the most relevant outcome of reflux monitoring studies is esophageal acid exposure and the role of symptom indices in patient management is unclear. Similarly, except in unusual circumstances where the pharmacological effectiveness of PPIs is in question, reflux monitoring studies should be done withholding PPI therapy for a week prior to (and during) the study to best address the question "does my patient have pathological GERD?" [54].

Esophageal high-resolution manometry

Esophageal high-resolution manometry (HRM) has no direct role in diagnosing GERD. However HRM can be useful to identify conditions that can facilitate or exacerbate reflux (hiatal hernia, hypotensive EGJ, ineffective esophageal contractions), to identify GERD mechanisms (TLESR, strain), or to diagnose conditions that can mimic GERD (rumination syndrome). Esophageal manometry is also usually performed before pH-metry or pH-impedance monitoring to localize the LES for probe positioning. Finally, manometry is required prior to antireflux surgery to verify the adequacy of peristaltic function and to rule out major motility disorders (achalasia) masquerading as GERD [70].

Barium swallow

Similar to manometry, barium radiography has minimal role in the diagnosis of GERD, but can be useful to identify conditions associated with GERD (hiatal hernia) or anatomical complications that may have bearing on treatment (e.g. short esophagus, stricture, paraesophageal hernia). A recent study reported that barium swallow alone had a sensitivity of 73% to detect hiatal hernia, the same as endoscopy, while HRM had a sensitivity of 92% and a specificity of 93% [71].

Mucosal impedance

Reflux injury to the esophageal mucosa makes it more permeable to ions and small molecules, which in turn alters its resting electrical impedance as can be measured during reflux monitoring studies or with a probe passed through the instrument channel of an endoscope. Recent reports suggest that measurement of esophageal mucosal impedance might be useful to diagnose GERD [72]. An Italian study proposed measuring baseline impedance during the overnight period of 24-hour pH-impedance monitoring studies reporting that a mean nocturnal baseline impedance <2446 Ω was predictive of GERD, defined as PPI-responsive heartburn, with a sensitivity of 98% and a specificity of 79% in a cohort of 120 patients without esophagitis [73]. In another cohort of 52 patients (16 with esophagitis, 19 NERD, and 17 functional heartburn) baseline impedance <2100 Ω had a sensitivity of 78% and a specificity of 71% for GERD [74]. An alternative method to measure baseline esophageal impedance is with a probe passed through the working channel of an endoscope