The Diagnosis of Gastroesophageal Reflux Disease

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ABSTRACT

BACKGROUND: Gastroesophageal reflux disease is a highly prevalent condition that imposes a significant economic impact on the US health care system. The utility of commonly used tests for the diagnosis of gastroesophageal reflux disease has not been adequately reviewed.

METHODS: A comprehensive review of the literature was undertaken to provide an evidence-based approach to the diagnosis of gastroesophageal reflux disease. EMBASE (1980-December 2008), OVID MEDLINE, and PubMed, (1966-December 2008) were searched using "gastroesophageal reflux" and "adults" with other terms, including medications, diagnostic tests, symptoms, and epidemiologic terms. Studies were limited to human trials, English language, and full articles.

RESULTS: Heartburn is a reasonably sensitive symptom for the diagnosis of gastroesophageal reflux disease, although it does not reliably predict esophagitis. Standardized questionnaires have limited specificity, whereas the double-contrast barium swallow has a low sensitivity to diagnose gastroesophageal reflux. The role of esophageal manometry is limited to accurate placement of a pH-measuring device. pH testing has reasonable sensitivity and specificity for the diagnosis of gastroesophageal reflux disease. The sensitivity of upper endoscopy to diagnose gastroesophageal reflux is lower than that of pH tests.

CONCLUSION: The diagnosis of gastroesophageal reflux disease remains difficult. In the absence of alarm symptoms, empiric treatment with acid suppression is warranted. pH testing provides valuable information in many patients, although the clinical utility of newer tests needs to be determined. Endoscopy should not be the first test used to diagnose gastroesophageal reflux.

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KEYWORDS: Acid reflux; Bravo pH capsule; Esophageal manometry; Esophagus; Gastroesophageal reflux disease; Impedance; pH probe; Proton pump inhibitor

Gastroesophageal reflux disease is the most common outpatient gastroenterology diagnosis in the United States, with a prevalence of 10% to 20% in the western world and an annual incidence of 0.38% to 0.45%.[1-9] Currently, several definitions are used to diagnose gastroesophageal reflux disease (Table 1), although none have been prospectively validated.[10-14] The major physiologic causes of gastroesophageal reflux include an increased number of transient lower esophageal sphincter relaxations, ineffective esophageal motility, and reduced lower esophageal sphincter tone.[15,16] Risk factors for gastroesophageal reflux disease include obe-

sity; the presence of a hiatal hernia; and the use of estrogen, nitrates, anticholinergics, and tobacco products.[16-18]

Gastroesophageal reflux disease reduces health-related quality of life[19,20] and imposes a significant economic burden on the US health care system.[21,22] Esophageal complications of untreated or undertreated gastroesophageal reflux are listed in Table 2.[16,23]

Although diagnostic tests are used routinely to evaluate patients with suspected gastroesophageal reflux disease, considerable controversy exists over how best to diagnose this prevalent disorder. The goal of this monograph is to provide a comprehensive review on the diagnosis of gastroesophageal reflux disease, including an evaluation of the clinical utility of commonly used tests.

MATERIALS AND METHODS

Literature Search

A search of the published literature using OVID MEDLINE, PubMed, and EMBASE databases was performed. For Ovid MEDLINE and PubMed (1966 to December 2008), "gastroesophageal reflux" (English language) was combined (using the "AND" operator) with "adults," followed by additional search terms, including "diagnosis," "reflux," "heartburn," "questionnaires," "diagnosis," "symptoms," "medications," "esophageal manometry," "pH-metry," "Bravo pH capsule," "impedance," "barium studies," "radiology," "endoscopy,"

> ## CLINICAL SIGNIFICANCE
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> - Gastroesophageal reflux disease is highly prevalent, with rates approaching 20% in the western world.
> - Gastroesophageal reflux reduces patients' quality of life and imposes a significant economic impact on the US health care system.
> - A number of tests are now available to help diagnose gastroesophageal reflux; however, their utility is unclear.

and "esophagogastroduodenoscopy." Similar search terms were used for EMBASE (1980 to December 2008). Results were limited to human trials, English language, adults, and full articles. References within studies that met selection criteria were manually searched for other potentially relevant studies.

Utility of Symptoms to Diagnose Gastroesophageal Reflux Disease

Heartburn and regurgitation are the cardinal symptoms of gastroesophageal reflux disease. Heartburn describes the sensation of discomfort or burning behind the sternum rising up into the neck, made worse after meals or on reclining, and eased by antacids.[13] Regurgitation is defined as the perception of flow of refluxed gastric contents into the mouth or hypopharynx.[13] Symptoms often occur in clusters, and patients frequently cannot define a predominant symptom.[24]

The accuracy of heartburn and regurgitation in the diagnosis of gastroesophageal reflux disease is difficult to define, limited by the lack of a gold standard for the diagnosis of gastroesophageal reflux disease. Furthermore, many languages do not have a direct translation for the word "heartburn," and studies are not available examining unselected populations with heartburn and correlating symptoms with both endoscopy and pH monitoring.[13] A recent systematic review identified 7 studies (n = 5134) that assessed the accuracy of reflux symptoms in the diagnosis of esophagitis.[25] The sensitivity (30%-76%) and specificity (62%-96%) of reflux symptoms were generally disappointing in diagnosing endoscopically proven esophagitis. Other studies confirm these results.[26-28]

Commonly, chest pain, chronic cough, symptoms of chronic laryngitis, and asthma are observed among patients

Table 1 Gastroesophageal Reflux Disease Defined

Genval Workshop Report (1999)[10]
> Individuals exposed to the risk of physical complications from gastroesophageal reflux or those who experience clinically significant impairment of health-related well-being (quality of life) because of reflux-related symptoms, after adequate reassurance of the benign nature of their symptoms.

Canadian Consensus Conference (2004)[11]
> The reflux of gastric contents into the esophagus causing symptoms sufficient to reduce quality of life or cause injury. Endoscopy negative reflux disease applies to individuals who have gastroesophageal reflux disease and normal endoscopy findings.

American College of Gastroenterology (2005)[12]
> Symptoms or mucosal damage produced by the abnormal reflux of gastric contents into the esophagus.

Montreal Definition (2006)[13]
> A condition that develops when reflux of gastric contents causes troublesome symptoms or complications.

American Gastroenterological Association (2008)[14]
> Montreal definition adopted.

Table 2 Complications of Gastroesophageal Reflux

Esophageal	Extra-esophageal
Esophagitis	Hoarseness
Esophageal ulcers	Laryngitis
Peptic stricture	Laryngeal nodules
Barrett's esophagus	Laryngeal cancer
Adenocarcinoma	Globus
Asthma	Chronic cough
	Chronic bronchitis
	Pulmonary fibrosis
	Pneumonitis
	Chest pain (noncardiac)
	Dental erosions

with esophagitis or reflux symptoms.[2,29-31] The reported odds ratios for these extraesophageal symptoms among patients with gastroesophageal reflux disease ranged from 1.2 to 3.0, with nocturnal cough and chest pain having the strongest association. Meta-analyses find a high probability of chest pain responding to aggressive acid suppression,[32] thereby proving causality, but this is not the case for similar analyses for asthma, hoarseness, or cough.[33,34]

The symptom of heartburn is reasonably sensitive in that it is expressed by a majority of patients defined as having gastroesophageal reflux disease on the basis of an abnormal pH study result or the finding of esophagitis on endoscopy. However, heartburn does not reliably predict esophagitis and cannot consistently distinguish gastroesophageal reflux disease from dyspepsia, another highly prevalent disorder of the upper gastrointestinal tract.[28,35]

DIAGNOSING GASTROESOPHAGEAL REFLUX DISEASE WITH A STANDARDIZED QUESTIONNAIRE

Researchers have developed multiple questionnaires to improve the accuracy of diagnosing gastroesophageal reflux; however, many have limitations that preclude routine use (Table 3).[26,36-50] Some have been validated in only 1 language, whereas others have not been directly compared with

Table 3 Questionnaires Used to Diagnose Gastroesophageal Reflux Disease

Author	Year	No. of Questions	Sensitivity	Specificity
Greatorex and Thorpe[37]	1983	6	NR	NR
Locke et al[38,a]	1994	80	NR	NR
Carlsson et al[39]	1998	7	92%	19%
Shaw et al[40,b]	2001	22	NR	NR
Elola-Olasu et al[41c]	2002	80	NR	NR
Numans and de Wit[26,d]	2003	7	48%-73%	50%-73%
Wong et al[42,e]	2003	20	82%	84%
Wang et al[43,e]	2004	3	79%-96%	35%-69%
Chinese Study Group[44,e]	2004	4	94%	50%
Zimmerman[45]	2004	5	89%	94%
Shimoyama et al[46,f]	2005	9	80%	54%
Horowitz et al[47]	2007	15	70%-75%	63%-78%
Ho et al[48,g]	2008	6	77%	51%

NR = not reported.
[a]This questionnaire is commonly referred to as "GERQ."
[b]Study distilled initial 22 questions to 12.
[c]Validated in a Spanish population.
[d]Carlsson-Dent questionnaire used and compared with esophagogastroduodenoscopy.
[e]Validated in a Chinese population.
[f]Validated in a Japanese population.
[g]Modified Carlsson-Dent questionnaire-reported sensitivity and specificity are for the English version.

endoscopy or a pH study.[38,40-44,46] Many have limited sensitivity and specificity.[26,48-50] Although a questionnaire would seem to be the perfect instrument to diagnose gastroesophageal reflux disease, no questionnaire has become the gold standard because of complexities in symptom description, symptom breadth, and cross-cultural differences. In addition, poor specificity hampers diagnostic accuracy.

UTILITY OF RADIOLOGIC STUDIES

Fluoroscopic studies are considered positive for the diagnosis of gastroesophageal reflux disease if reflux is witnessed during the examination or there is morphologic evidence of reflux esophagitis (ie, a finely nodular or granular-appearing mucosa). Overall, the double-contrast esophagram is thought to have a limited role in detecting gastroesophageal reflux.[51,52] A non-systematic review of 10 fluoroscopic studies using different techniques (n = 587) found that gastroesophageal reflux was observed in just 35% of symptomatic patients.[53] Provocative maneuvers, such as the water-siphon test, increased the sensitivity of the barium test from 26% to 70%.[54]

Two studies have compared the double-contrast esophagram to ambulatory pH monitoring in patients with reflux symptoms. One small study (n = 11) found that all patients with reflux at or above the thoracic inlet had pathologic reflux on recumbent pH monitoring,[55] whereas a larger study (n = 112) found that 30% of patients with an abnormal ambulatory transnasal pH study result had radiographically diagnosed esophagitis, compared with 10% with a normal pH study result (P < .05).[56]

Double-contrast barium studies of the esophagus are useful if the goal of the study is to define the anatomy of the esophagus or to identify complications of gastroesophageal reflux.[52,57-59] The sensitivity of a barium swallow to detect gastroesophageal reflux is low if a provocative maneuver is not used.

ROLE OF UPPER ENDOSCOPY

Endoscopic findings in patients with gastroesophageal reflux disease include esophagitis, erosions and ulcers, strictures, and Barrett's esophagus. However, most individuals with gastroesophageal reflux disease symptoms have normal endoscopic examination results and are considered to have either nonerosive reflux disease or a condition other than reflux (ie, functional dyspepsia).[60,61] Although the sensitivity of esophagogastroduodenoscopy for the diagnosis of gastroesophageal reflux disease is lower than that of 24-hour pH-metry, the specificity for diagnosing mucosal injury is excellent.[62]

Many patients with uncomplicated gastroesophageal reflux symptoms undergo treatment with an acid suppressant before endoscopic evaluation. A recent study randomized patients with uncomplicated gastroesophageal reflux disease (n = 612) to either empiric proton pump inhibitor therapy or endoscopy, followed by treatment based on mucosal findings.[63] Empiric therapy was more cost-effective without

negatively affecting patient health-related quality of life. Acid suppression before esophagogastroduodenoscopy may significantly limit the sensitivity of endoscopy as a diagnostic tool.

Interobserver agreement on the endoscopic assessment of reflux esophagitis has been shown to be acceptable, and the extent of esophageal acid contact time seems to be related to the grade of esophagitis and the presence of complications.[64] Although endoscopic determination of the grade of esophagitis can predict the expected healing response to antisecretory agents and the need for effective maintenance regimens,[65] the treatment of gastroesophageal reflux disease is typically guided by symptoms, and thus determination of the grade of esophagitis for most clinical situations is not necessary.[14]

The role of newer endoscopic technologies—including narrow band imaging, chromoendoscopy, confocal endomicroscopy, magnification and high-resolution endoscopy, capsule endoscopy, and ultra-thin, unsedated transnasal endoscopy—for the diagnosis of gastroesophageal reflux disease is controversial, primarily because of a lack of comparison with other validated tests.[66,67]

Upper endoscopy should not be the first test used for the diagnosis of gastroesophageal reflux disease. A recent therapeutic trial of a proton pump inhibitor makes it even more unlikely to find erosive changes consistent with a diagnosis of gastroesophageal reflux disease.

ROLE OF ESOPHAGEAL MANOMETRY

Esophageal manometry is used commonly during the evaluation of patients with dysphagia, chest pain, and gastroesophageal reflux disease. Manometry assesses peristalsis and contractile pressures in the body of the esophagus, in addition to measuring resting tone and relaxation of both the lower and upper esophageal sphincters (Figure 1).

Esophageal manometry is clinically indicated to diagnose achalasia, assist in the placement of pH probes, evaluate patients with symptoms of dysphagia, and evaluate patients with chest pain after sufficient empiric treatment for gastroesophageal reflux disease.[68] Esophageal manometry should not be used to make or confirm a diagnosis of gastroesophageal reflux.

One study evaluated the utility of esophageal manometry.[69] In this prospective study (n = 286), esophageal manometry was most likely to change patient diagnosis in those referred for dysphagia (51%) compared with those referred for noncardiac chest pain (38%) or reflux symptoms (25%; $P < .05$).

The role of esophageal manometry in patients with reflux symptoms is to assist in the placement of a pH-measuring device.[68] As a diagnostic tool, esophageal manometry cannot make a diagnosis of gastroesophageal reflux disease for the simple reason that it does not measure acid reflux. The clinical utility of high-resolution manometry has not been studied in patients with gastroesophageal reflux.[70]
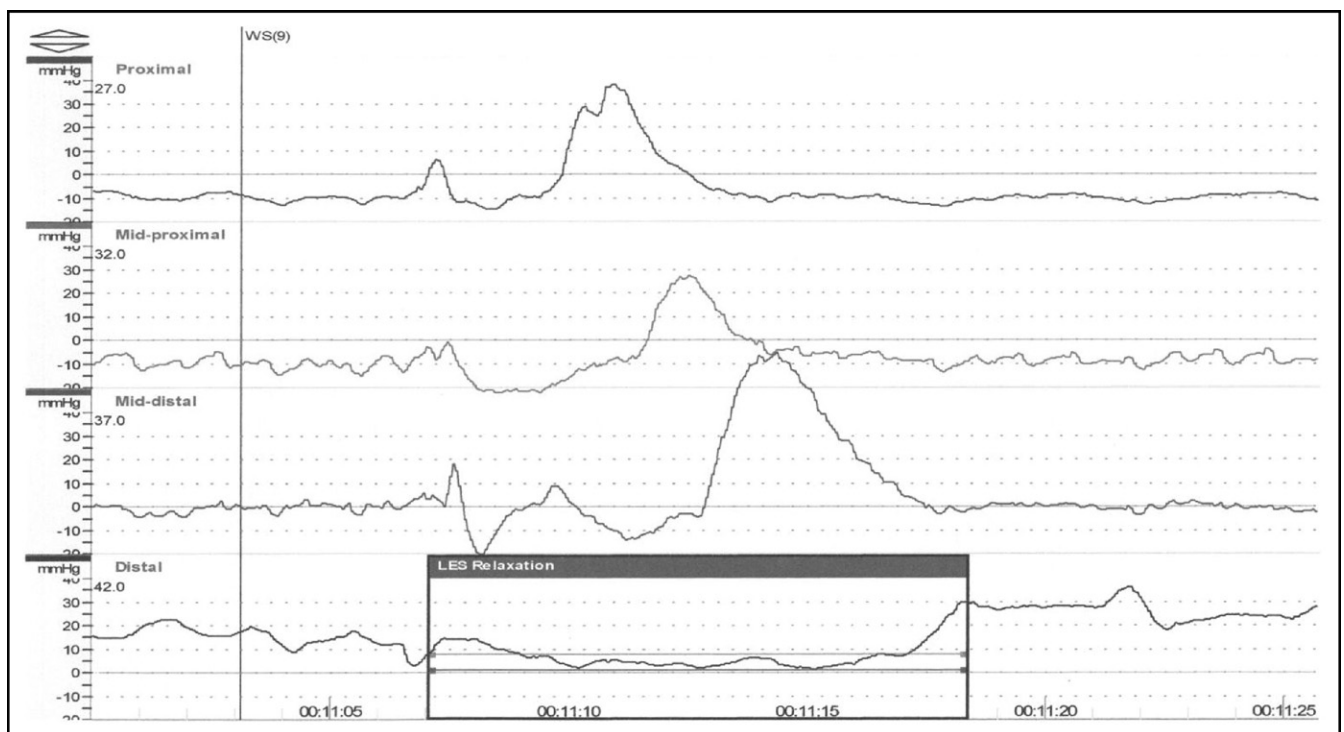

Figure 1   Tracing of normal esophageal motility study using a solid-state catheter. The patient swallows water, and a peristaltic wave develops in the proximal esophagus and propagates through the mid and lower esophagus (top 3 panels). The lower esophageal sphincter (bottom) relaxes normally with the water swallow. The x-axis is time (in seconds), and the y-axis is amplitude (in millimeters of mercury). WS = water; LES = lower esophageal sphincter.

UTILITY OF TRANSNASAL pH PROBES AND IMPEDANCE-pH

Esophageal pH monitoring was first used in 1969, and the first systematic analysis of esophageal acid exposure was published in 1974.[71,72] Food and Drug Administration clearance followed in 1984. Most ambulatory pH probes contain a small antimony electrode attached to an external digital data-logger. The electrode is passed transnasally and positioned 5 cm above the upper border of the lower esophageal sphincter (Figure 2). The sensitivity and reproducibility of the 24-hour test (81%) are better than in tests of shorter duration.[73]

Ambulatory impedance monitoring was first introduced in 1991 and approved by the Food and Drug Administration in 2002. The impedance probe uses a series of electrode rings positioned along the catheter to measure the electrical conductance of refluxed material.[74] This device measures esophageal exposure to gastroduodenal contents and when combined with a pH probe (impedance-pH) can determine whether gastric refluxate is acidic (pH < 4), weakly acidic (pH 4-7), or non-acidic (pH > 7) in nature.[74] The test seems to produce valid and reproducible data.[75]

The original role of esophageal pH testing was to diagnose gastroesophageal reflux disease in patients with reflux symptoms but normal upper endoscopy findings. However, the empiric use of proton pump inhibitors has changed the role of diagnostic testing in gastroesophageal reflux disease.[14,76,77] Objective testing is now used to identify patients who do not respond to acid suppressants and to verify the diagnosis of gastroesophageal reflux disease before fundoplication.[14]

Ambulatory 24-hour pH monitoring has acceptable sensitivity (77%-100%) and specificity (85%-100%) in patients with endoscopically proven esophagitis; however, the test is rarely indicated in this situation. The sensitivity (0%-71%) and specificity (85%-100%) are more varied in those with endoscopy-negative gastroesophageal reflux disease.[77] On the basis of a consensus statement for impedance monitoring,[78] and by using both manometry and pH monitoring as comparators, this test has a sensitivity and specificity of greater than 90% and is considered to be the best tool available to test reflux–symptom association. However, the clinical utility of either device in those refractory to empiric proton pump inhibitor therapy remains elusive.

Ambulatory pH testing is safe, inexpensive, and fairly accurate at diagnosing esophageal acid reflux. The sensitivity for diagnosing endoscopy negative reflux disease, which is thought to represent an acid-sensitive esophagus, is lower. On or off proton pump inhibitor therapy pH testing for a patient refractory to therapy is currently controversial.[79,80] Positive test findings *off* therapy suggest the presence of reflux but do not reliably answer why the patient is refrac-
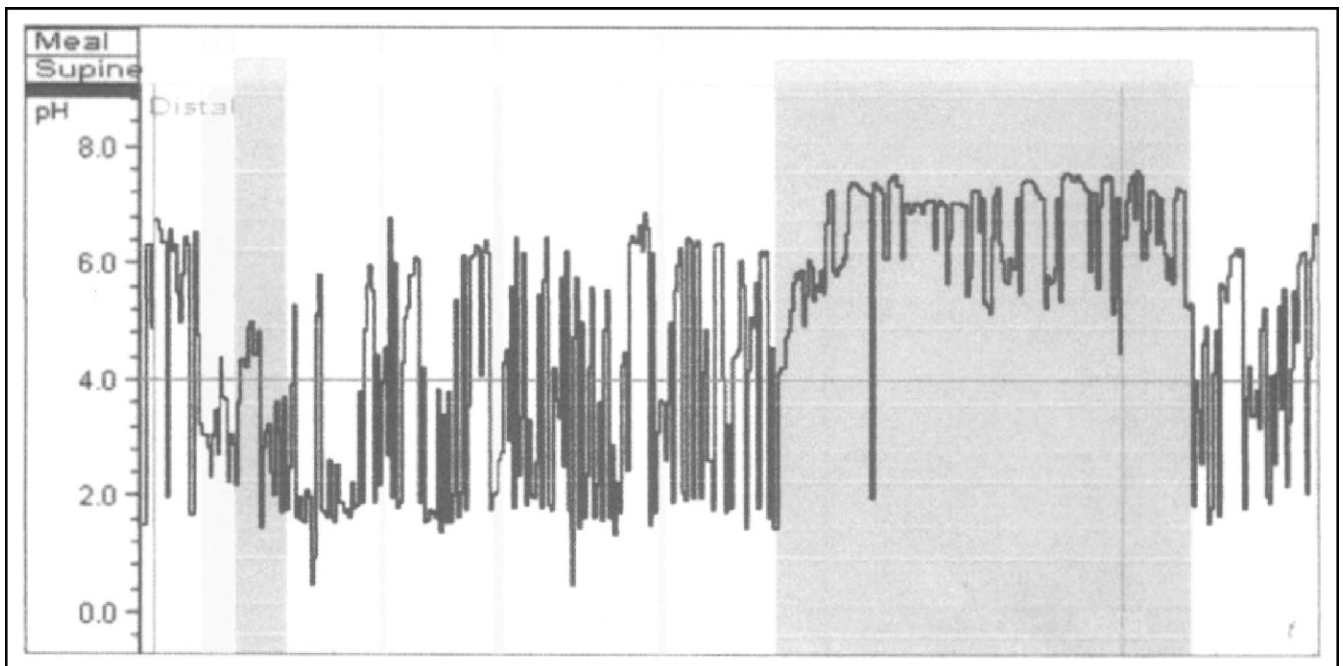

Figure 2   Twenty-four hour pH probe recording from a patient with reflux symptoms. This study was performed *off* of proton pump inhibitor therapy. The pH probe is positioned 5 cm above the mid-portion of the lower esophageal sphincter. The x-axis is time, and the y-axis shows pH levels. The faint gray block background (4 individual sections) indicates the time when the patient ingested a meal; this portion of the study is excluded from data analysis. The white background indicates upright time, and the dark gray background (~1 hour on the left side of the diagram and ~8 hours on the right side of the diagram) indicates supine time. This study shows acid exposure predominantly in the upright position. Note the near absence of reflux in the nocturnal supine position (indicated by the dark gray area on the right side of the diagram).

Figure 3 Bravo pH capsule (Givens; Yoqneam, Israel) placed in the distal esophagus, 5 cm proximal to the gastroesophageal junction.

the squamocolumnar junction using endoscopy or 5 cm above the proximal aspect of the lower esophageal sphincter using manometry.[82] pH data (Figures 3 and 4) are transmitted to an external receiver via a radiofrequency signal. The performance of the Bravo wireless pH electrode in measuring distal esophageal acid exposure has been validated and found to be a useful substitute for conventional transnasal catheter-based pH systems.[81,83] Sedation does not seem to affect test characteristics.[82]

Tolerability is better with the wireless system compared with catheter-based pH monitoring in both randomized and uncontrolled comparison studies.[84,85] Studies can now be performed *off* and then *on* therapy during extended time periods.[86] Extending the study period also has the potential benefit of increasing the yield of symptom reflux correlation. As an example, with the use of distal esophageal acid exposure time, 12.4% of patients would have been miscategorized as not having acid reflux if only 24 hours of recording were analyzed instead of 48 hours. The clinical utility of the Bravo pH capsule (n = 309 patients) seems to be high because results of the Bravo pH capsule frequently changed both patient management (64%) and diagnosis (22%).[87] A decision model analysis of a hypothetic managed care organization found that timely use of the Bravo pH capsule reduced unnecessary proton pump inhibitor use and medication costs.[88]

The wireless Bravo pH monitoring system is a safe, readily available, validated alternative to catheter-based pH monitoring. It is the diagnostic test of choice for patients who cannot tolerate traditional pH-catheter placement and those who require a longer duration of pH monitoring. Forty-eight hours of recording increases the diagnostic accuracy of identifying patients with acid reflux who are mistakenly classified as normal using only 24 hours of pH recording. Limitations include the cost of the capsule, the

tory to therapy. Conversely, positive test findings on therapy do not imply symptom correlation given the lack of outcome studies. Negative findings using either device in a patient refractory to therapy has a higher value.

UTILITY OF THE BRAVO PH CAPSULE

The Bravo pH monitoring system (Givens; Yoqneam, Israel) was developed to circumvent limitations of transnasal pH monitoring by substituting a wireless radiotelemetry pH recording capsule ($6 \times 5.5 \times 25$ mm) that attaches to the esophageal mucosa.[81] The capsule is positioned 6 cm above
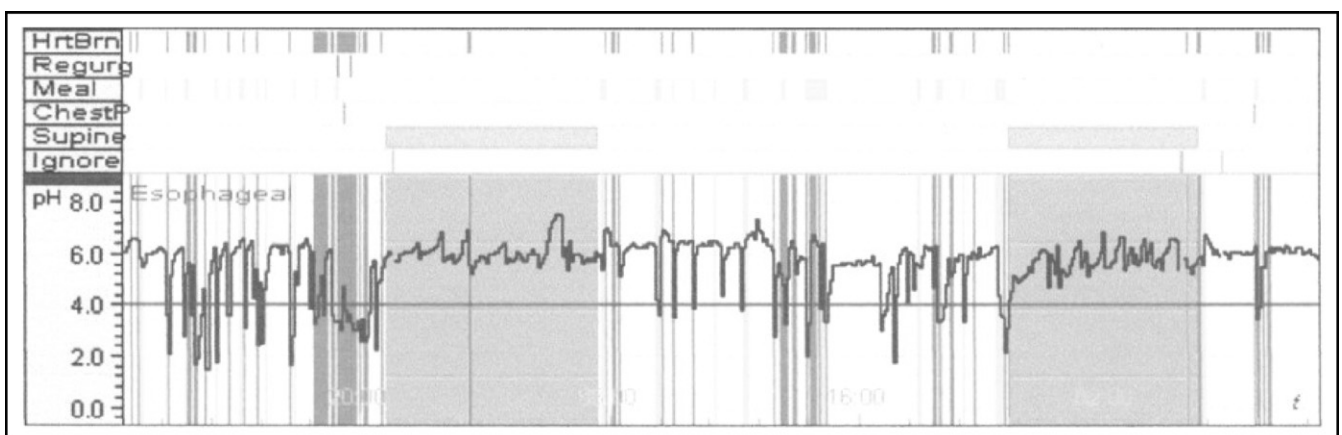

Figure 4 Bravo pH capsule recording. The Bravo pH capsule (shown in Figure 3) is positioned 5 cm above the squamocolumnar junction. The x-axis is time (in hours), and the y-axis denotes pH levels. Upright time is shown as a white background, and supine time is shown as a dark gray background. Symptoms of heartburn, regurgitation, and chest pain are indicated by vertical lines and were recorded by the patient so that symptoms can be correlated with acid reflux. Note that most acid reflux events occur in the upright position in this patient, whereas no acid reflux occur in the supine (dark gray background) position.

ability to only measure acid reflux, and the rare need for upper endoscopy to remove the capsule because of severe chest pain.[85] Considerable controversy exists whether Bravo pH testing should be performed *on* or *off* proton pump inhibitor therapy.

UTILITY OF EMPIRIC ACID SUPPRESSION IN THE DIAGNOSIS OF GASTROESOPHAGEAL REFLUX DISEASE

Many clinicians currently use the response to a proton pump inhibitor therapeutic trial as evidence for the presence or absence of gastroesophageal reflux disease. The accuracy of a proton pump inhibitor therapeutic trial in diagnosing gastroesophageal reflux disease is similar to that of 24-hour pH monitoring.[89] A variety of proton pump inhibitor doses have been studied in patients with symptoms suggestive of gastroesophageal reflux disease or noncardiac chest pain.[36,63,90-95] In patients with laryngeal manifestations of gastroesophageal reflux disease, the doses ranged from 40 to 80 mg omeprazole daily.[96-98] The most commonly used proton pump inhibitor has been omeprazole, which led to the term "omeprazole test."[36,90-93] However, studies using other proton pump inhibitors have demonstrated that they are equally as efficacious.[94,95]

An important factor in determining the sensitivity of a proton pump inhibitor therapeutic trial is the definition of a positive test. In most studies, a symptom score cutoff was used. If the symptom assessment score for heartburn, chest pain, or other symptoms improved by more than 50% to 75% relative to baseline (depending on the study), the test was considered positive. Studies rarely calculated the receiver operator curve.[36,90,99]

Assessment of the diagnostic accuracy of the proton pump inhibitor therapeutic trial in patients with symptomatic gastroesophageal reflux disease or nonerosive reflux disease is limited by the lack of a gold standard for diagnosing gastroesophageal reflux disease. The proton pump inhibitor therapeutic trial has minimal utility in patients with erosive esophagitis, whereas its value increases in patients in whom the likelihood of a specific syndrome being attributed to reflux is low (ie, hoarseness). The proton pump inhibitor therapeutic trial has been shown to be fairly sensitive (68%-92%) and specific (36%-100%) in diagnosing gastroesophageal reflux disease-related noncardiac chest pain.[90,92,93] Two separate meta-analyses concluded that the proton pump inhibitor therapeutic trial reduces chest symptoms and is useful as a diagnostic tool in identifying gastroesophageal reflux disease-related noncardiac chest pain with an overall sensitivity of 80% (95% confidence interval [CI], 71%-87%) and a specificity of 74% (95% CI, 64%-83%).[32]

In contrast, the specificity of the proton pump inhibitor therapeutic trial for patients with reflux symptoms (but without chest pain) was found to be relatively low. A meta-analysis of 15 studies that evaluated the value of the proton pump inhibitor therapeutic trial in patients with typical gastroesophageal reflux disease symptoms demonstrated that short-term treatment with a proton pump inhibitor (1-4 weeks) does not confidently establish the diagnosis of gastroesophageal reflux disease.[100] The sensitivity and specificity of the proton pump inhibitor therapeutic trial were 78% and 54%, respectively. The low specificity may be due to a therapeutic response by some patients diagnosed with functional heartburn. Also, a subset of these patients may respond to a proton pump inhibitor therapeutic trial because their underlying mechanism for heartburn is hypersensitivity to normal levels of gastroesophageal reflux.[36,92]

A proton pump inhibitor therapeutic trial is a safe, simple, and noninvasive diagnostic tool for patients thought to have gastroesophageal reflux disease-related noncardiac chest pain. It can be a powerful diagnostic tool for clinicians when evaluating and treating patients with different manifestations of gastroesophageal reflux disease and offers significant cost-savings when compared with other diagnostic tools.[36,90] Patients with persistent symptoms of gastroesophageal reflux who do not respond to a proton pump inhibitor trial should be evaluated for gastroesophageal reflux using pH testing as described.

CONCLUSIONS

This review highlights the fact that the diagnosis of gastroesophageal reflux disease remains problematic. The high prevalence of this disorder, combined with its significant negative economic impact on the health care system, mandates that we become better equipped to diagnose gastroesophageal reflux disease. To begin, a global consensus must be reached on how to define gastroesophageal reflux disease. Next, a simple and reliable questionnaire that can accurately diagnose gastroesophageal reflux needs to be developed. In addition, a large prospective multinational study is needed to evaluate and compare the utility of diagnosing gastroesophageal reflux disease with questionnaires, upper endoscopy, impedance-pH probes, and the Bravo pH capsule. Finally, all diagnostic studies need to be critically evaluated with regard to their clinical utility.

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