

PRACTICE GUIDELINES

ACG Practice Guidelines: Esophageal Reflux Testing

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Investigations and technical advances have enhanced our understanding and management of gastroesophageal reflux disease. The recognition of the prevalence and importance of patients with endoscopy-negative reflux disease as well as those refractory to proton pump inhibitor therapy have led to an increasing need for objective tests of esophageal reflux. Guidelines for esophageal reflux testing are developed under the auspices of the American College of Gastroenterology and its Practice Parameters Committee and approved by the Board of Trustees. Issues regarding the utilization of conventional, catheter-based pH monitoring are discussed. Improvements in the interpretation of esophageal pH recordings through the use of symptom-reflux association analyses as well as limitations gleaned from recent studies are reviewed. The clinical utility of pH recordings in the proximal esophagus and stomach is examined. Newly introduced techniques of duodenogastroesophageal reflux, wireless pH capsule monitoring and esophageal impedance testing are assessed and put into the context of traditional methodology. Finally, recommendations on the clinical applications of esophageal reflux testing are presented.

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ACG Guidelines on the clinical applications of ambulatory esophageal pH monitoring were last published 10 yr ago (1). Since that time, research investigations and technical advances have enhanced our understanding of both the utility and limitations of this diagnostic modality. Studies have examined whether placement of pH probes in the pharynx, cervical esophagus, and proximal stomach yield information that alters the management of gastroesophageal reflux disease (GERD). Newer techniques for esophageal functional testing such as wireless pH capsule monitoring, duodenogastroesophageal (formerly referred to as alkaline or bile reflux) reflux detection, and esophageal impedance testing have been introduced over the past decade and are currently available in clinical practice. A recent, prospective study compared the indications for esophageal pH monitoring in clinical practice with the indications in practice guidelines (2, 3). Less than half of the studies performed were in accordance with the recommendations. Two studies reported that pH testing resulted in a change in management in approximately 50% of investigated patients, although such changes were maintained in only half of the cohort (4, 5).

This second practice guidelines summarizes advances in GERD diagnostic testing and how they have modified the clinical management of esophageal disorders. A literature search was conducted for English-language articles dealing with functional evaluation of the esophagus from 1994 to 2006. Databases included Medline and PubMed with

search terms that included esophageal pH monitoring, GERD, esophageal impedance, asthma, laryngitis, chest pain, Bilitec, and bile reflux.

ESOPHAGEAL AMBULATORY pH MONITORING

Technical Aspects

WIRELESS pH MONITORING. First introduced over 30 years ago, catheter-based esophageal pH recording remains both a widely accepted and available technique for quantifying esophageal acid exposure. The technique has been extensively examined and critically reviewed in earlier clinical guidelines (1,2). The most significant recent technical advance in pH recording has been the incorporation of the antimony electrode into a wireless capsule that transmits pH data to an external receiver via radiofrequency telemetry (433 MHz). The current data sampling at 6-s intervals of the wireless pH capsule (Bravo system, Medtronic, Minneapolis, MN) (0.17Hz) is slower than the 4-s intervals used by the Slimline pH catheter systems (0.25Hz) (Medtronic, Minneapolis, MN) and 5-s intervals used by the Sandhill pH catheter system (0.20 Hz) (Sandhill Scientific, Highlands Ranch, CO). Prior studies have demonstrated that faster sampling frequencies up to 1 Hz lead to the detection of a greater total number of reflux events but do not change the overall acid exposure values (6). Using the wireless pH system, the 95th percentile for distal esophageal acid exposure for control subjects was 5.3%, a value higher than values reported in several although not all catheter-based system studies (2, 7, 8). The higher acid exposure threshold reported in healthy controls using the wireless pH system may be the consequence

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of less restriction in daily activities or the result of a thermal calibration error that existed in the pH catheter systems. Both of these issues will now be addressed.

A major advantage of the wireless pH system is patient tolerability. Nasally passed pH electrodes are both uncomfortable and conspicuous leading patients to avoid potentially reflux provoking stimuli such as meals and physical activity (9). However, a second study from Spain reported that patients' dietary, sleep, and tobacco use did not vary during the performance of pH studies, although 65% of patients did report diminished physical activity (10). Wong *et al.* randomized 50 patients to either catheter-based or wireless pH monitoring and reported less interference with daily activity and improved overall satisfaction with the pH capsule (11). Taking advantage of the improved patient comfort with the wireless pH system, Pandolfino *et al.* demonstrated a three-fold increase in acid exposure during physical exercise compared with nonexercise periods (12). Therefore, pH recordings using the wireless pH system improve patients' ability to perform their daily activities and thus provide a more accurate picture of their acid exposure profile as well as improve their compliance with the study.

COMPARISON OF WIRELESS pH CAPSULE AND CATHETER-BASED pH RECORDINGS. During studies simultaneously using the wireless pH and Slimline catheter pH systems, a significant offset was noted in the pH values reported by the two systems (13–15). As a result of this offset, the Slimline system reported a median percent time pH <4 of 3.5% in a group of healthy subjects compared with 1.75% with the wireless pH system. Swallowed orange juice with pH of 3.88 measured *ex vivo* using a benchtop pH glass electrode was used as a reference standard and demonstrated that the wireless pH system gave a median pH value of 3.84 compared with 3.11 for the Slimline catheter. This difference in calibration has been determined to be due to a thermal calibration correction factor error inherent to the Slimline software. This error has since been corrected. Another difference noted between the wireless pH capsule and Slimline catheter was in the detection of number of acid reflux events. The Slimline recorded a significantly greater number of events that could only partly be explained by the thermal correction factor error

(14). The difference was due to a higher detection of short reflux episodes and likely secondary to the lower sampling rate of the wireless pH compared with Slimline catheter system. It should be noted that both the wireless pH and Slimline systems miss a proportion of short reflux events due to their sampling frequencies being lower than the optimal frequency of 1 Hz (6). Whether the short reflux episodes are associated with symptoms and may affect the sensitivity of symptom association of pH testing with the wireless pH system is uncertain. Moreover, such short events do not alter the overall acid exposure times.

LIMITATIONS OF WIRELESS pH TESTING. Disadvantages of the wireless pH system exist. The current capsule size does not allow for reliable nasal passage such that oral passage of the delivery catheter is necessary. Endoscopy is generally performed immediately prior to wireless pH capsule placement to determine the position of the squamocolumnar junction, thereby adding cost to the procedure. Early capsule detachment prior to 24 h is uncommon but can add additional costs for incomplete data acquisition. In one report, 12% of capsules failed to attach properly on first attempt necessitating a replacement capsule. Modifications to the catheter delivery system have since been performed by the manufacturer. A second report from two centers reported capsule detachment prior to 16 h in 3/85 subjects and prior to 36 h in 9/85 subjects (7). Detachment that occurs during the 48-h recording period could lead to erroneous interpretation of the acid exposure time consequent to intragastric pH recording (Fig. 1). This potential error can be minimized by manual inspection of the pH tracing as well as querying the patient regarding the timing of loss of esophageal foreign body sensation. Finally, a single case report described a proximal esophageal perforation following an attempted wireless pH capsule placement (17). Serious complications including perforation have not been reported in the published series totaling over 850 subjects (7, 12, 13, 15, 16, 18–25).

Additional drawbacks are minor. The validity of using the squamocolumnar junction as a reference point for the gastroesophageal junction has not been subject to the same scrutiny as the manometric positioning of the catheter-based pH electrodes. However, prior studies have demonstrated

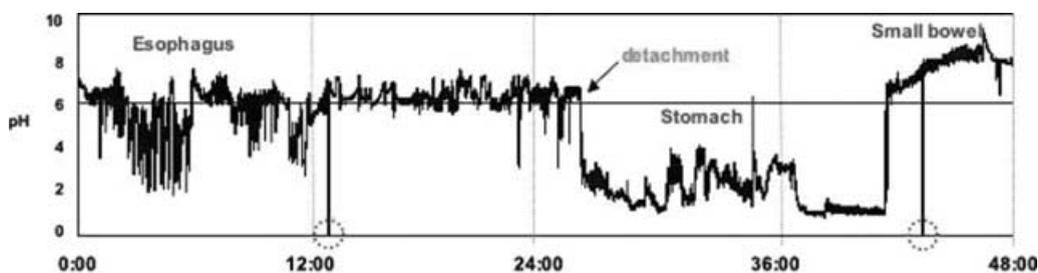


Figure 1. Early detachment of the wireless pH capsule in a GERD patient. Note the sudden prolonged drop in pH representing the capsule in the stomach and then the sharp rise as the capsule enters the small intestine through the pylorus. In addition, there are two small areas indicating data loss (dotted circles).

consistency of the positioning of the proximal margin of the lower esophageal sphincter (LES) 1 to 1.5 cm above the squamocolumnar junction (26). The reliability of using other markers such as the proximal margin of the gastric folds in patients with Barrett's esophagus has not been determined. Patient discomfort from the pH capsule has been reported with many patients noting a foreign body sensation, especially with deglutition (21, 22). This is generally of little consequence with rare patients requiring early capsule removal by endoscopy secondary to discomfort (7, 11). Manometric studies have recorded high amplitude foci of esophageal body contractions in the vicinity of the pH capsule that may account for symptoms of chest pain in some patients (27). Inadequate data reception resulting in periods of missing data is most commonly the result of the receiver being out of range of the capsule. Modifications to the hardware have reduced this problem and the current software automatically deletes such periods from the final analysis. Finally, failure of capsule detachment, albeit rare, can necessitate endoscopic extraction.

OPTIMAL DURATION OF pH MONITORING. The standard duration of recording for esophageal pH testing is 24 h. With the introduction of the wireless pH system, prolonged recording periods extending beyond 24 and even 48 h are now both well tolerated and feasible. The wireless pH system routinely records for 48 h although early detachment prior to 48 h occurs in about 10% of patients (7, 19). The 48-h data could be interpreted using an average of the 2 days or only the 24-h period with the greatest acid exposure (worst day analysis). A significant increase in the sensitivity of pH testing and small decrease in specificity were evident when utilizing the worst day data compared with either the initial 24-h or overall 48-h data in comparing controls with GERD patients. Defining GERD as the presence of erosive esophagitis and an abnormal pH study as greater than 5.3% exposure time, the sensitivity of day 1 testing was 74% and specificity 90%. By using the worst day of the 2-day recording window, the sensitivity increased to 100% with a decrease in specificity to 85% (7). A similar increase in reflux detection was recently reported for a 2-day compared with single-day reflux study using the wireless pH system (22). Of note, earlier catheter-based studies examining the reproducibility of pH testing over two different study days reported concordance of between 73 and 89% (28, 29). The differences in lifestyle and dietary factors that likely account for this variability are reduced by the prolonged recording window with the wireless pH system.

A shorter recording period utilizing the pH catheter system has been proposed as an accurate means of assessing reflux that allows for improved patient tolerance. Arora and Murray described a 3-h postprandial pH test in a series of patients with GERD and reported a sensitivity of 88% and specificity of 98% using the results of the entire 24-h ambulatory study as the reference standard (30). Although this may be an alternative for some patients, the wireless pH capsule circumvents many of the tolerability problems of catheter-based studies. Furthermore, the 24- to 48-h recording windows allow for

assessment of supine and upright patterns of reflux as well as increased detection of symptoms for symptom association calculations (31).

pH ELECTRODE CALIBRATION. Calibration is performed on all pH systems prior to each study using reference buffer solutions. An analysis of 100 consecutive pH studies using posttest calibration testing of catheter-based antimony pH electrodes found drift of greater than 0.4 pH units in 5% and a change in study interpretation in 6% of studies when the drift was factored into the final analysis (32). Posttest calibration is currently not routinely performed for clinical studies with the wireless pH capsule due to the *in vivo* fixation of the capsule that does not allow for posttest immersion into buffer solutions. Recently, a protocol involving the use of swallowed juice has been reported (13, 14, 19). This method involves measuring the pH of orange juice or a similar acidic beverage using a benchtop glass pH electrode. The juice is then swallowed and the nadir pH is recorded on the wireless pH device both at the beginning and termination of the study period. This technique has been validated in comparisons with catheter-based pH electrodes both *in vivo* and *ex vivo*. Calibration drift can be corrected prior to final data analysis. However, the optimal manner by which to recalculate data that is obtained in the setting of a significant pH baseline drift has not been determined. Therefore, the utility of posttest calibration for the wireless pH capsule has not yet been determined and is currently not routinely performed. For catheter-based pH recordings, posttest calibration is easily performed and analysis should factor in large deviations in the baseline pH measurements.

OPTIMAL pH ELECTRODE LOCALIZATION. Catheter-based pH electrodes are by convention positioned 5 cm above the proximal border of the LES. This localization minimizes potential artifact that could result from catheter migration into the proximal stomach during swallowing but may not be the optimal site to maximize the sensitivity of pH testing. Using videoradiography, pH probe migration by up to 2 cm cephalad as well as 2 cm caudad was observed during deglutition (33). Furthermore, improper positioning of the pH catheter electrode has been detected by fluoroscopic imaging in up to 5% of patients due to buckling of the catheter in either the pharynx or esophagus (34). Inadvertent pH probe migration into the proximal stomach has also been reported, presumably as a result of slippage of the nasal fixation.

As would be expected given effects of gravity, esophageal peristalsis, and salivary buffering, proximal esophageal acid exposure is significantly less than distal exposure (35). In a study by Fletcher *et al.*, esophageal acid exposure was over six times greater with a pH catheter fixed by means of metal clips at 0.5 cm compared with 5.5 cm above the LES (36). Positioning the pH electrode immediately above the squamocolumnar junction has theoretical advantages in that the endoscopic changes of reflux esophagitis are typically most apparent at this level and not 5 cm above the proximal border of the LES.

Currently, the wireless pH capsule is positioned 6 cm above the squamocolumnar junction, which closely approximates the conventional pH electrode positioning of catheter-based pH studies (13). A potential advantage of the wireless pH capsule is its ability to be affixed to the mucosal wall in closer proximity to the squamocolumnar junction. A study of nine patients with GERD compared acid exposure profiles of a capsules affixed 1 cm and 6 cm above the squamocolumnar junction (37). Significantly greater acid exposure times were recorded with the 1-cm probe, most apparent in the postprandial period where the acid exposure times were nine times greater at the 1-cm compared with 6-cm site. While this may improve the sensitivity of pH monitoring in the diagnosis of GERD, the technique needs to be validated and will likely compromise test specificity to some extent. Thus, at this time, conventional positioning of the wireless pH capsule 6 cm above the squamocolumnar junction and catheter electrode 5 cm above the proximal LES are recommended for clinical studies.

pH TESTING: ON- VERSUS OFF-PROTON PUMP INHIBITOR (PPI) THERAPY. Presently, controversy exists as to whether pH testing is more useful when performed with patients on or off PPI therapy. Testing off-therapy is often recommended for patients in whom there is a low index of suspicion for reflux disease, to “rule out GERD” on the basis of quantitatively normal esophageal acid exposure. A negative pH study performed with the patient off PPI therapy is generally considered evidence that a patient does not have pathologic reflux disease, especially when combined with a negative symptom correlation measure. Off-therapy testing is also utilized to document the presence of reflux in patients without esophagitis who are being evaluated for antireflux endoscopic treatment or surgical fundoplication. A limitation of off-therapy pH testing is the interpretation of an abnormal study. Off-therapy pH testing may demonstrate abnormal reflux but this does not indicate causality between the reflux and the patient’s symptoms. Symptom–reflux correlation using a symptom index (SI) can help but can also be inaccurate in the setting of frequent reflux episodes that result in a high SI on the basis of chance associations. The symptom association probability (SAP) is a better statistical method that can limit misinterpretation of false-positive chance associations. The yield of the SI and SAP is greater when done off- rather than on-PPI therapy.

On-therapy testing is more commonly used to evaluate patients with refractory reflux symptoms. The intent is to investigate the possibility that an individual patient is having persistently abnormal distal esophageal acid exposure in spite of PPI therapy. Evidence of significant reflux events on PPI therapy, although uncommon, is used to support the use of more aggressive medical, endoscopic, or surgical therapies for GERD (2, 38). The likelihood of having an abnormal pH study on PPI therapy is variable and depends upon the clinical setting and indication for which the test is being performed. On twice-daily PPI therapy, only 4% of patients had abnormal

pH monitoring in one study (39). Another recent study reported much higher failure rates of 50% of patients who were asymptomatic on PPI therapy, three quarters of whom were on b.i.d. PPI therapy (40). Even if the overall percentage of patients with persistent acid reflux on PPI therapy is small, one could argue that pH monitoring is still of clinical utility to identify the population of truly refractory patients who may benefit from additional medical, endoscopic, or surgical therapy. A potential limitation of on-therapy testing is that the reduction in gastric acidity converts acid to weakly acid or nonacid reflux episodes that are not detected by pH monitoring. The clinical importance of such episodes is a matter of current controversy best addressed through ongoing investigations using esophageal impedance monitoring.

The threshold acid exposure time for an abnormal pH study done on PPI therapy is not established. While the conventional, off-therapy thresholds of percent time pH <4 of 4–5% have been commonly used, Kuo and Castell suggested a more stringent cutoff of 1.6% based on the 95% confidence interval using a pH catheter-based study of healthy controls treated with omeprazole 40 mg (41). Whether the relative rather than absolute decrease in acid exposure time off and on PPI therapy is relevant for symptom relief has not been determined. Furthermore, assessment of symptom association with reflux episodes on therapy may be more relevant than the actual percent time of distal acid exposure.

A recent study took advantage of the prolonged recording capabilities of the wireless pH system to allow for pH monitoring both off and on PPI therapy in a single test (19). Patients with suspected GERD underwent wireless pH testing off PPI therapy for the first 24 h followed by three additional recording days on rabeprazole 20 mg PO b.i.d. (Fig. 2). Two wireless pH receivers were calibrated to a single pH capsule to allow for the prolonged recording. All patients had demonstrable reductions in distal esophageal acid exposure by day 3 with only 5% failing to normalize acid exposure values by day 4. Early capsule detachment that prevented complete analysis on therapy occurred in 5%. By combining pH monitoring both off and on therapy, two distinct questions can be answered in a single study: (a) Does the patient have abnormal distal esophageal acid exposure consistent with GERD? and (b) If reflux is present, is it being suppressed by PPI therapy? The prolonged recording period can also increase the sensitivity for the detection of symptoms for correlation with reflux episodes (31). A disadvantage of this 4-day protocol is the lower sensitivity for the diagnosis of GERD afforded by the 24-h rather than 48-h recording period off therapy. Studies with the wireless pH system have demonstrated an increase in test sensitivity between 12 to 25% when incorporating the 48-h recording period (7, 31). To circumvent this limitation, a 48-h-off and 48-h-on PPI therapy protocol is being investigated but could be limited by failure to achieve a steady-state PPI effect on acid secretion or visceral sensitivity. In addition, early capsule detachment, although uncommon, may be an issue especially in patients in whom the on-therapy data are considered more important than off-therapy data.

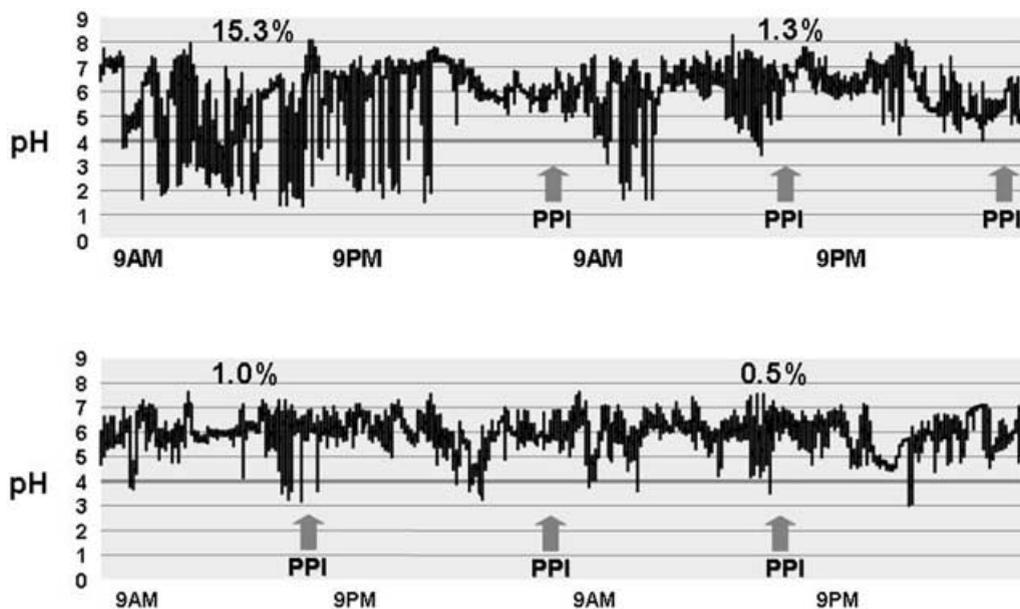


Figure 2. Ninety-six-hour wireless pH recording combining periods both off and on PPI therapy from a patient with significant GERD. Initial esophageal exposure was 15.3% on day 1 and demonstrated an upright reflux pattern. Following the administration of rabeprazole at 20 mg PO b.i.d., the acid exposure decreased to 1.3% on day 2, 1.0% on day 3, and 0.5% on day 4.

Data Analysis

An advantage of the 24-h pH test over other diagnostic modalities is the ability to correlate symptoms with acid exposure events. Multiple methods have been devised to use statistical calculations to correlate symptoms with acid reflux. The first scheme was the SI (42). This involves dividing the number of symptoms associated with pH <4 by the total number of symptoms yielding a percentage of symptom episodes that correlate with GERD. Symptom indices can be separately calculated for each symptom attributable to reflux including heartburn, regurgitation, or chest pain. Analysis using receiver operating characteristic curves designed to optimize sensitivity and specificity derived a value of 50% as the optimal threshold for a positive SI for patients with multiple episodes of heartburn (43). The SI has important limitations. It does not take into account the total number of reflux episodes. Thus, a patient with multiple reflux episodes but only one symptomatic reflux event will have an SI of 100%. Reporting the SI as a ratio of events as well as percentage circumvents this limitation. However, in patients with frequent reflux episodes, random, temporal associations between reflux and symptoms may produce a high SI in the absence of any true association. The second devised scheme was the symptom sensitivity index (SSI) (44). This involves dividing the total number of reflux episodes associated with symptoms by the total number of reflux episodes. This system is also limited and failed to take into account the total number of symptom episodes. The proposed scheme with the best statistical validity for symptom–reflux correlation is the symptom probability analysis (SAP) (45). This involves constructing a contingency table with four fields: (a) positive symptom, positive reflux; (b) negative symptom, positive re-

flux; (c) positive symptom, negative reflux; and (d) negative symptom, negative reflux. The Fisher's exact test is then applied to calculate the probability that the observed association between reflux and symptoms occurred by chance. Therefore the SAP determines the statistical validity of symptom–reflux associations while the SI and SSI provide data on the strength of the association. An SAP value of >95% indicates that the probability that the observed association between reflux and the symptom occurred by chance is <5%.

Attempts have been made to validate the utility of the symptom indices. Two groups have reported that patients with a high SI but normal esophageal acid exposure time respond better to PPI therapy than patients with a low index (46, 47). Prakash and Clouse reported that the use of a 2-day recording window with the wireless pH system allowed for increased detection of symptom events, thereby improving the reflux-associated symptom probability analysis (31). Arguing against the usefulness of the indices, Taghavi *et al.* prospectively compared the SI, SSI, and SAP using a symptom response to high-dose omeprazole as a relatively objective independent measure defining reflux disease (48). All three indices performed poorly in predicting the response to PPI therapy. The sensitivities of the SI, SSI, and SAP in comparison to the omeprazole test were 35%, 74%, and 65% while the specificities were 80%, 73%, and 73%, respectively. This observation highlights limitations in not only the indices but also the lack of a diagnostic standard for defining symptomatic reflux disease.

A major shortcoming in using any of the available symptom indices is in the completeness by which patients record their symptom events. Symptoms may occur as prolonged rather than transitory events, which can lead to inaccuracies

in their association with short-lived pH drops. On the other hand, symptom indices rely on correlation with acid reflux events that may go undetected with less frequent sampling rates of currently used pH monitoring systems. Furthermore, it should be emphasized that the utilization of symptom association depends upon the specific symptom being analyzed. Interpretation of reflux association with heartburn is more straightforward than cough or other laryngeal symptoms. Cough can be induced by reflux but can also cause reflux via an increase in the gastroesophageal pressure gradient. Laryngeal symptoms are generally chronic symptoms that may not demonstrate direct association with individual reflux episodes.

Overall, symptom indices add an important dimension to the interpretation of pH monitoring. While the percent time pH >4 indicates whether abnormal degrees of acid reflux are present, it does not indicate causality between the reflux and an individual patient's complaints. Likewise, normal degrees of acid reflux may still be clinically significant if they are strongly associated with symptoms. The SI has intuitive appeal and is readily calculated. The SAP is more statistically robust and is now included on automated analysis routines on currently available pH analysis software systems. However, as none of the symptom association schemes have been well validated, they should currently be viewed as complementary information that statistically links a particular symptom to reflux events but does not guarantee response to medical or surgical antireflux therapies.

Investigators from Italy have reported on a new parameter by which to analyze esophageal acid exposure. Instead of using a fixed parameter of percent time pH <4, the authors used the area under the curve of hydrogen ion activity (49, 50). Such methodology accounts for not only the duration of acid exposure but also the degree of esophageal acidification, with greater significance placed on a pH value of 2 compared with 3, for example. In a study of 30 controls and 60 patients with GERD, the authors reported an increase in diagnostic sensitivity by 17% for nonerosive and 10% for erosive GERD (50). Additional studies have demonstrated a correlation between esophagitis grade and magnitude of integrated esophageal acidity (51). The integrated esophageal acidity is not calculated on currently available data analysis programs for clinical practice and its clinical utility is still being investigated.

Intra-gastric pH Monitoring

Intra-gastric pH recording is most commonly performed by placement of a pH probe 10 cm below the proximal margin of the LES. This manometrically guided placement results in positioning of the probe in the gastric fundus (52). An esophageal sensor 5 cm above the LES simultaneously records esophageal acid exposure. Limited studies have shown an association between esophagitis healing with intra-gastric acidity (53). Studies done using gastric pH monitoring have demonstrated that intra-gastric pH control on PPI therapy as defined by maintenance of pH >4 is poor. Single-

dose PPIs maintain the intra-gastric pH >4 less than 50% of the time while b.i.d. dosing only results in approximately 70% control (54). The greatest proportion of acid exposure has been demonstrated at night leading to the term "nocturnal acid breakthrough" or NAB. NAB has been arbitrarily defined as intra-gastric pH <4 for more than 1 h in the overnight period in patients on PPI therapy. The phenomena have been demonstrated in over 50–80% of both healthy subjects and patients with GERD (54–57). *Helicobacter pylori* infection is a factor in many individuals and can decrease the frequency of NAB as well as increase the intra-gastric acid control of PPI therapy (57). Recently, cytochrome P450 genotype status has been shown to correlate with the degree of control of daytime acid as well as nocturnal gastric acid breakthrough that occurs with PPI therapy or PPI therapy combined with an H2 receptor antagonist. Extensive or rapid PPI metabolizers benefit from higher doses of PPI or addition of an H2RA for more complete gastric acid suppression (58).

Controversy has been generated not as to whether NAB exists but rather its clinical relevance to GERD. Studies have reported disparate findings concerning whether intra-gastric acid exposure is an adequate predictor of esophageal acid exposure (56, 59, 60). Esophageal reflux occurs during periods of NAB in only 6% of healthy subjects and 20% of patients with uncomplicated GERD (52, 54). Additional studies have confirmed a poor correlation between NAB and both symptoms of GERD as well as esophageal reflux episodes (56, 60–62). Esophageal motility parameters including a hypotensive LES and low amplitude esophageal body contractions may be associated with a higher degree of acid reflux during NAB although this has not been confirmed by all investigators (40, 63). Presence of hiatal hernia and competency of the gastroesophageal junction are variables that may increase the significance of NAB in increasing esophageal acid exposure.

There exist a number of limitations to intra-gastric pH monitoring using pH probes. The most important limitation is the inability of the electrode to ascertain the volume of acidic contents. This is less important in esophageal monitoring given the limited volume available in the esophageal lumen. Small volumes of gastric acid that would be expected to have little impact on risk of esophageal reflux cannot be distinguished from large volumes. Additional limitations in accuracy include interactions of ingested food, differential compartmentalization of gastric contents within the stomach, neutralization of gastric acid by duodenal bicarbonate, and potential loss of electrode contact due to gas in a distended stomach. Substantial inter- and intraindividual variability have been reported in both baseline intra-gastric acidity measurements in contrast to more uniform values obtained with esophageal pH monitoring (60, 64). Following potent acid-suppressing therapy, percent time intra-gastric pH <4 can vary between 0 to over 90% (56, 60). This substantial inter- and inpatient variability limits the utility of the technique in the assessment of an individual patient. Therefore, the evidence supporting the clinical significance and applicability of gastric pH

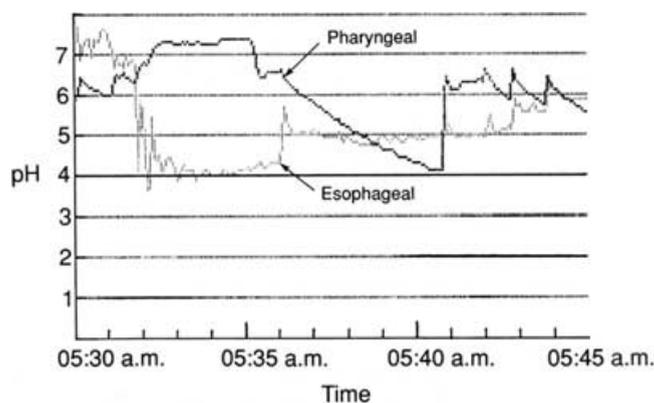


Figure 3. Example of a pseudo-reflux event. A gradual drop in pharyngeal pH with a rapid upward recovery is not associated with a simultaneous drop in esophageal pH. This is most likely an artifact and most commonly seen during recumbent sleep periods.

monitoring is insufficient to recommend its routine use in clinical practice.

Proximal pH Recording

Acid reflux into the proximal esophagus or pharynx has been associated with supraesophageal or aerodigestive manifestations of GERD that include chronic laryngitis, chronic cough, and asthma. A number of studies have examined these associations using pH probes positioned in a variety of locations, most commonly 15 or 20 cm above the proximal margin of the LES. Proximal esophageal pH detection may also serve as an indirect marker for the volume of gastroesophageal reflux (65). Proximal recordings are often done to accommodate the use of a dual-probe pH catheter so that the distal probe can be positioned for monitoring distal esophageal reflux in the conventional position 5 cm above the LES. Unfortunately, such “blind” placement does not position the proximal probe in a uniform location relative to the upper esophageal sphincter (UES). In a prospective analysis of 661 proximal pH studies, in 9% of subjects, the proximal probe was in the hypopharynx, 55% in the cervical esophagus, and 36% at the upper esophageal sphincter (66). Concurrent pH recordings at 3, 5, 9, 12, and 15 cm above the LES have demonstrated a linear decrease in the acid exposure times emphasizing the importance of electrode positioning (67).

Additional limitations exist. A downward drift in pH values in the pharynx without a corresponding decrease in distal esophageal pH has been attributed to an artifact of drying of the electrode referred to as “pseudo-reflux” (68–70) (Fig. 3). Sensitivity of pharyngeal pH recording is further compromised by buffering of refluxed acid by swallowed salivary and airway bicarbonate secretion. Using manometry to position the proximal pH electrode 2 cm above the UES, Williams *et al.* reported that 67% of proximal reflux events were artifacts, occurring independently of distal esophageal acidification (69). This same group proposed that more stringent criteria be used to define pharyngeal reflux: (a) magnitude of change of pH >2 units, (b) nadir pH <4.0, (c) abrupt pH

decrease (onset of pH decrease to nadir <30 s to exclude pseudo-reflux), and (d) pH decrease occurring during a period of distal esophageal acidification (69). Variability in the reproducibility of proximal reflux recording has been demonstrated. In one study examining intrasubject reproducibility of recordings made on two separate days, abnormal proximal acid reflux pH values were reproducible in only 55% of studies in contrast to 82% for distal reflux (71).

With these limitations in mind, a number of investigators have reported normative data for proximal pH recordings in healthy subjects without either typical or extraesophageal reflux symptoms. The 95th percentile for the upper limit of normal for total pharyngeal acid exposure time was less than 1% (72, 73). Normal values for proximal esophageal acid reflux based on a sensor positioned 15 cm above the LES have been reported as less than 1.1% (71). Values of less than 0.9 and 1.4% have been reported for pH electrodes positioned 20 cm above the LES (74, 75). However, it should be noted that the clinical utility of these values is controversial. Whether the percent time pH <4 or the absolute number of reflux episodes is a more valid criterion for the diagnosis of pathologic amounts of proximal reflux is uncertain. Some investigators consider even a single pharyngeal reflux event accompanied by a drop in distal esophageal pH as abnormal (68, 76). In light of these limitations and controversies, the available evidence does not support the routine use of proximal pH monitoring in clinical practice.

DUODENOGASTROESOPHAGEAL REFLUX MONITORING

Previously referred to as alkaline or bile reflux, duodenogastroesophageal reflux encompasses the esophageal reflux of duodenal contents that may include biliary secretions, pancreatic enzymes, and bicarbonate. Earlier studies examined the detection of intraluminal esophageal pH values of >7 as a surrogate marker of duodenogastroesophageal reflux. However, more recent studies have questioned the validity of equating the detection of alkaline pH rises in the esophagus with reflux and have suggested other mechanisms including salivary and esophageal bicarbonate secretion may be the origin of such events (77). The past decade has seen advances in the detection of bilirubin allowing for more direct measure of duodenal reflux, obviating the need for alkaline pH detection. Bechi *et al.* developed and validated the use of a fiberoptic sensor to detect bile based on its spectrophotometric absorption properties that led to the development of the ambulatory Bilitec system (Metronic Instruments, Minneapolis, MN) (78). Aspiration studies have correlated bilirubin reflux event detection and both bile acid and pancreatic enzyme activity (78, 79). The potential clinical importance of bile reflux is supported by animal models that have demonstrated that conjugated bile acids at acidic pH and unconjugated bile acids at a more alkaline pH may cause mucosal damage (79). Two important limitations of bile acid reflux monitoring are an underestimation of bile reflux when the refluxate is of pH

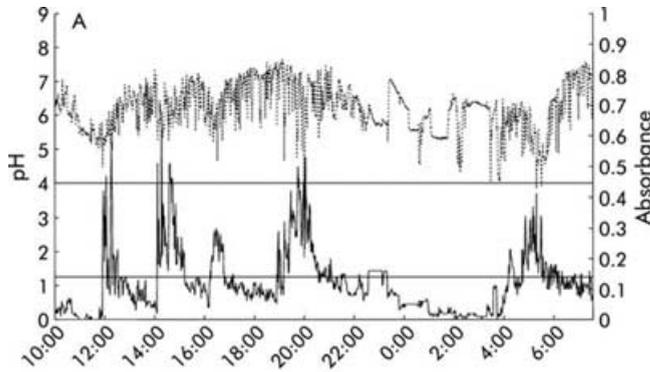


Figure 4. Combined pH and bile acid reflux monitoring studies in a patient with typical reflux symptoms during omeprazole 20 mg twice-daily treatment, showing normal acid exposure and pathological duodenal reflux exposure. The x axis depicts time, the left y axis depicts intraesophageal pH, and the right y axis depicts bilirubin absorbance. Cutoffs of the normal ranges are indicated (pH <4; bilirubin absorbance >0.14).

less than 3.5 and the need for patients to avoid ingesting substances that might lodge in the sampling chamber or that have an absorbance characteristic similar to bile.

Bile acid reflux monitoring has increased our understanding of the importance of duodenogastroesophageal reflux. Using combined bile acid reflux and ambulatory pH monitoring, Vaezi *et al.* demonstrated that combined acid and bile reflux was the most common reflux pattern in patients with GERD (60, 80). Duodenal gastroesophageal reflux (DGER) occurred in 50% of patients with NERD, 79% of patients with erosive esophagitis, and 95% of patients with Barrett's esophagus. The majority of bile reflux events occurred concomitantly with acid reflux. Similar conclusions have been reported by Marshall *et al.* who also reported an inverse symptom association with bile reflux events in patients with GERD, supporting the conclusion that acid rather than bile is the dominant factor responsible for GERD symptoms (81). Several groups have demonstrated that treatment with PPI therapy markedly reduced the occurrence of both acid as well as bile reflux (82–84).

With the recognition that DGER closely tracked with acid reflux and could be suppressed with PPI therapy, enthusiasm for the use of bile acid reflux monitoring in clinical practice waned. Tack *et al.*, however, have recently published a series of studies suggesting a possible role for DGER in both symptoms and esophagitis in a subset of patients with difficult to manage, symptomatic reflux. In the first study, 65 patients with persistent heartburn and regurgitation on single-dose PPI therapy underwent simultaneous pH and bile acid reflux monitoring on PPI therapy (85). Surprisingly, 51% of patients had erosive esophagitis on endoscopy despite the fact that they were on PPI therapy at the time of the study. DGER was almost twice as common as acid reflux in this select population. More symptoms occurred in association with bile than acid reflux. Furthermore, when patients with erosive esophagitis were compared with patients with nonerosive

disease, the former had less pure acid reflux and greater combined acid and bile reflux. A second study by the same group examined the effectiveness of baclofen in patients with continued symptoms as well as a negative pH study and positive bile acid reflux study while taking b.i.d. PPI therapy (Fig. 4) (86). In this carefully selected group of patients with symptoms refractory to PPI therapy, baclofen 20 mg PO t.i.d. significantly reduced the DGER exposure as well as symptoms of heartburn. Three major limitations to the generalizability of this study include the small sample size, uncontrolled protocol, and lack of the use of direct symptom association to correlate the refractory symptoms with DGER events. Because of the latter concern, it is unclear whether the benefits of baclofen were actually due to a reduction in DGER. The data in this provocative study need to be substantiated before therapy directed at DGER should be recommended for refractory reflux patients. Furthermore, baclofen at such doses is commonly associated with significant side effects that include excessive somnolence that limits its clinical use.

ESOPHAGEAL IMPEDANCE TESTING

Intraluminal impedance monitoring detects the occurrence of changes in the resistance to electrical current across adjacent electrodes positioned in a serial manner on a catheter assembly. It is capable of differentiating the antegrade and retrograde bolus transit of both liquid and gas. Multiple electrodes are positioned along the axial length of the impedance catheter such that the proximal extent of a reflux event can be determined. Impedance monitoring is not able to detect either the acid content or volume of the intraluminal contents. Therefore, a pH electrode is typically incorporated into the recording assembly. Additional limitations of impedance monitoring include low baseline impedance values generated by the mucosa of Barrett's esophagus and esophagitis that make detection of liquid reflux problematic in such circumstances. Inaccuracies in the current automated analysis software require manual data correction (87).

By nature of its ability to detect both acid as well as nonacid reflux, impedance–pH monitoring has greater sensitivity than pH monitoring alone in the detection of gastroesophageal reflux. The sensitivity of the method has been compared with reflux detection by esophageal manometry using common cavity as a surrogate marker and acid reflux by esophageal pH monitoring. In both healthy subjects and patients with GERD, impedance detected 92–99% of reflux by manometry and 97–98% of acid reflux by pH testing (88–90). Impedance monitoring is generally combined with pH monitoring to allow for the characterization of the refluxate into categories of acid, weakly acid, and weakly alkaline reflux (Fig. 5) (91, 92). Weakly acidic reflux has been defined as a reflux event associated with a concomitant drop in esophageal pH to between 4 and 7 and weakly alkaline reflux as an impedance detected reflux event not associated with a pH drop below 7 (91). A recent, multicenter study examined the impedance-characteristics of 60 healthy subjects during 24-h ambulatory

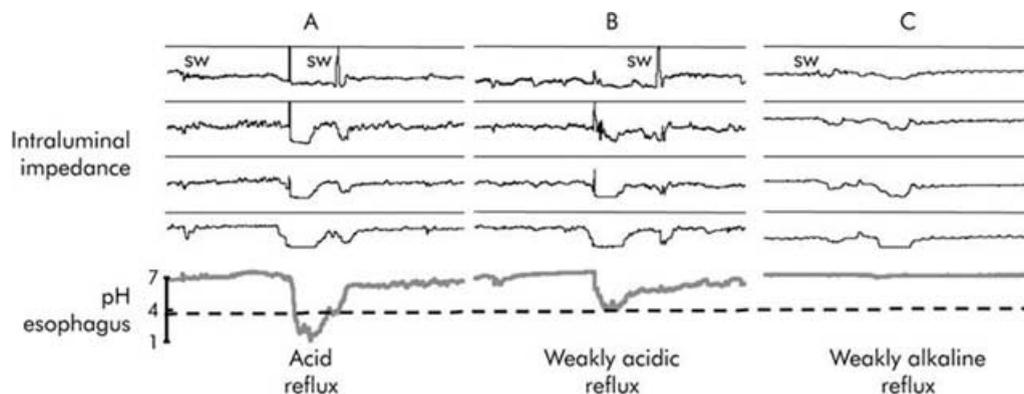


Figure 5. Definitions of reflux as defined by impedance changes are further characterized based on the pH of the refluxate. Acid reflux (*A*) is defined as reflux that reduces esophageal pH to below 4 or reflux that occurs when esophageal pH is already below 4. Superimposed acid reflux is a subcategory of acid reflux. Weakly acidic reflux (*B*) is defined as a pH fall of at least 1 unit where the pH falls between 4 and 7. Weakly alkaline reflux (*C*) is defined as a reflux episode during which nadir esophageal pH does not drop below 7.

monitoring (89). Based on impedance values 5 cm above the LES, the median number of total reflux episodes per 24 h was 30, the majority of which occurred in the upright position. Approximately two-thirds of the episodes were acid and another third weakly acidic reflux. Weakly alkaline reflux was distinctly uncommon in this healthy cohort. Similar frequencies were recently reported from a multicenter European study (93).

Impedance characteristics in patients with GERD demonstrate a similar frequency of overall reflux episodes compared with controls (94). Patients with GERD had significantly more acid reflux episodes compared with the controls, although there was substantial overlap between the two groups. No difference was shown in the frequencies of weakly acidic or nonacid reflux episodes. In an analysis of symptom association of 32 typical reflux patients off acid suppressant therapy, Bredenoord *et al.* demonstrated that the majority of symptomatic reflux events (85%) were associated with classically defined acid reflux and the minority (15%) with weakly acidic reflux (95). As shown in previous studies, these authors demonstrated that perception of acid reflux was dependent on the proximal extent, nadir pH, and magnitude of the pH drop of reflux events. In another study of 12 GERD patients, Vela *et al.* examined the effect of omeprazole on both acid and nonacid reflux (90). This was not an ambulatory study but a lab-based, 2-h protocol with patients kept in a right lateral decubitus position to maximize the occurrence of GERD following the ingestion of a refluxogenic meal. Patients were studied under the same protocol before and after a 7-day course of omeprazole 20 mg b.i.d. The total number of reflux episodes did not differ before or after PPI therapy. While the number of acid reflux events was nearly eliminated with omeprazole, the frequency of nonacid reflux events nearly doubled, accounting for the lack of change of overall reflux episodes. Interestingly, the overall frequency of symptomatic reflux events did not change with omeprazole. While the number of heartburn episodes decreased substan-

tially, the frequency of regurgitation symptoms increased. While the study concluded that impedance may be useful in evaluating the role of nonacid reflux in symptoms that persist on PPI therapy, the clinical significance of regurgitation in the absence of acid reflux is unclear. Clinical experience and overall patient responses in controlled trials of PPI therapy would suggest that it is the minority of symptomatic GERD patients who fail PPI therapy due to ongoing symptoms.

A recent study by Bredenoord *et al.* examined symptom associations between acid and nonacid reflux events using combined pH and impedance monitoring in 60 GERD subjects off PPI therapy (95). The proportion of patients with a positive SAP was greater with combined pH-impedance testing compared with pH testing alone (77% vs 68%). Although this absolute difference is not large, it does support an increased diagnostic sensitivity for testing using combined impedance and pH monitoring. It is important to note that the subjects in this study had typical reflux symptoms and were not patients who were refractory to PPI therapy. Furthermore, reflux symptoms used in the analysis included both heartburn and regurgitation. As demonstrated in the Vela *et al.* study, impedance monitoring may add to the sensitivity for detection of regurgitation but it is unclear from this study whether nonacid reflux is a clinically important explanation for refractory heartburn.

Several of these issues were addressed in two recent multicenter studies by Mainie *et al.* and Zerbib *et al.* that examined the utility of combined pH-impedance testing in subjects tested on b.i.d. PPI therapy (96, 97). One-half to two-thirds of the patients who reported symptoms during the 24-h recording period on PPI therapy had a negative symptom association, arguing against either acid or nonacid reflux as the cause of persistent symptoms in most patients studied on PPI therapy. In the Mainie *et al.* study that included patients who had failed b.i.d. PPI therapy, the demonstration of a positive SI for typical reflux symptoms was three times more common for nonacid than acid reflux (96). However, the positive symptom

Table 1. Recommendations for Ambulatory Esophageal pH, Impedance Monitoring, and Bile Acid Reflux Testing

pH monitoring is useful

1. Document abnormal esophageal acid exposure in an endoscopy-negative patient being considered for endoscopic or surgical antireflux procedure. An abnormal pH study does not, however, causally link reflux with a specific presenting symptom. Use of symptom association analyses provide information in this regard but have not been adequately validated.
2. Evaluation of endoscopy-negative patients with typical reflux symptoms that are refractory to PPI therapy.
 - a. pH study done on-therapy but consider extended testing with wireless pH system incorporating periods of both off- and on-therapy testing. The diagnostic yield of on-therapy testing in patients who have not symptomatically responded to b.i.d. PPI therapy is limited.
 - b. Use of a symptom correlation measure (SI, SSI, or SAP) is recommended to statistically interpret the causality of a particular symptom with episodes of acid reflux. Such measures can be applied even in the presence of esophageal acid exposure values that fall within the normal range. These statistical measures, however, do not ensure a response to either medical or surgical antireflux therapies. The yield of symptom association is increased when pH study is done for 48 h and off PPI therapy compared with 24 h and on PPI therapy, respectively.
 - c. Routine proximal or intragastric pH monitoring not recommended.

pH monitoring may be useful

1. Document adequacy of PPI therapy in esophageal acid control in patients with complications of reflux disease that include Barrett's esophagus. The threshold for adequate suppression of esophageal acid exposure on PPI therapy has not been defined. Furthermore, data supporting the clinical importance of achieving normalization of esophageal acid exposure in such patients are limited.
2. Evaluation of endoscopy-negative patients with atypical reflux symptoms that are refractory to b.i.d. PPI therapy. The diagnostic yield of pH testing under such circumstances is low.
 - a. pH study done on b.i.d. PPI therapy in patients with high pretest probability of GERD or off therapy in patients with low pretest probability of GERD. Pretest probability is based on prevalence of GERD in patient population under question, clinician's impression, and degree of response to empiric PPI trial. Consider extended pH study to incorporate periods both off and on PPI therapy.
 - b. Use of symptom correlation recommended for selected symptoms that include chest pain. Use of symptom correlation in the evaluation of chronic laryngeal symptoms, asthma, and cough is of unproven benefit.
 - c. Routine proximal or intragastric pH monitoring not recommended.

Combined pH monitoring with esophageal impedance monitoring may be useful

1. Evaluation of endoscopy-negative patients with complaints of heartburn or regurgitation despite PPI therapy in whom documentation of nonacid reflux will alter clinical management. The increased diagnostic yield of impedance monitoring over conventional pH monitoring for symptom association is highest when performed on PPI therapy and nominal off PPI therapy.
2. Utility of impedance monitoring in refractory reflux patients with primary complaints of chest pain or extraesophageal symptoms is unproven.
3. Current interpretation of impedance monitoring relies on use of symptom correlation measures (SI, SSI or SAP). The therapeutic implications of an abnormal impedance test are unproven at this time.

Bile acid reflux testing may be useful

1. Evaluation of patients with persistent typical reflux symptoms in spite of demonstrated normalization of distal esophageal acid exposure by pH study. Impedance monitoring may obviate the need for bile acid reflux testing under such circumstances.
2. Bile acid reflux testing equipment currently has very limited commercial availability.

association was predominantly noted for regurgitation rather than heartburn. In the study by Zerbib *et al.*, comparisons were made between separate cohorts that had pH–impedance testing done off and on PPI therapy. The increased diagnostic yield of combined pH–impedance testing beyond pH testing alone was lower when done off PPI therapy (4%) compared with on PPI therapy (17%) (97). Overall, these observations lend credence to the notion that mechanisms other than either acid or nonacid reflux are responsible for the majority of symptoms in patients failing to respond to high-dose PPI therapy. Combined impedance–pH testing is more sensitive than pH testing alone for the detection of nonacid reflux events associated with regurgitant reflux symptoms that persist on PPI therapy. Studies examining the benefits of treating nonacid and weakly acidic reflux are awaited to further substantiate the clinical importance of impedance testing.

CLINICAL APPLICATIONS

Suggested indications for ambulatory esophageal pH, impedance, and bile acid reflux testing in clinical practice are discussed and summarized in Table 1. Normative values for these tests are provided in Table 2.

Esophageal Manifestations of GERD

TYPICAL GERD. There is generally no indication for reflux testing in the majority of patients with GERD who derive adequate symptom relief with medical therapy. Furthermore, patients with complications of reflux including erosive esophagitis, peptic stricture, or Barrett's esophagus do not require pH testing to confirm the diagnosis. Two exceptions to this exist, one practical and the other yet unproven. The first is the documentation of abnormal acid reflux prior to the

Table 2. Normative Values for Esophageal pH, Impedance, and Bile Acid Reflux Monitoring

	Median	95th Percentile
Wireless pH capsule monitoring (% time pH <4/24 h)	2.0%	5.3% (7)
Esophageal impedance monitoring (episodes/24h)*		
Total reflux	30	73 (89)
Acid reflux	18	55
Weakly acidic reflux	9	26
Weakly alkaline reflux	0	1
Total nonacid reflux	9	27
Bile acid reflux monitoring (Percent time bilirubin absorbance level >0.14)	0.4	1.8% (80)

Current interpretation of impedance monitoring is not based on frequency of nonacid reflux events but upon symptom correlation measures (SI, SSI, SAP).

performance of endoscopic or surgical therapy for GERD or for the purpose of inclusion in a clinical trial of GERD therapy. While earlier studies focused on the inclusion of patients with erosive esophagitis, greater emphasis has recently been placed on inclusion of patients with nonerosive reflux disease. In the absence of a better disease definition for such patients, pH testing is an accepted diagnostic parameter. In light of this, recognition of the reduced sensitivity of pH testing in patients with nonerosive reflux disease is important. Several studies have demonstrated that pH testing has greater sensitivity in the setting of erosive rather than nonerosive reflux disease (2). Severity of erosive esophagitis has been positively correlated with the degree of distal esophageal acid exposure (98–103). Similarly, greater degrees of esophageal acid exposure are seen with complications of GERD including Barrett's, esophageal ulcers, and strictures (100). Conversely, milder grades of erosive esophagitis are more frequently associated with normal distal esophageal acid exposure. It is likely that the limited sensitivity of pH testing reported in studies of nonerosive reflux patients resulted from both inclusion of patients with symptoms that were not caused by acid reflux, *i.e.*, have functional heartburn, as well as diagnostic limitations of currently used pH monitoring methods.

A second potential though yet unproven indication for pH monitoring in GERD patients is in monitoring the adequacy of reflux control on medical therapy in asymptomatic patients with GERD complications. Greater degrees of distal esophageal acid exposure have been correlated with longer segments of Barrett's epithelium (104, 105). Studies have described a surprisingly high proportion of patients with Barrett's esophagus who fail to normalize their distal esophageal acid exposure in spite of PPI therapy (106). Compounding this problem is the observation that patients with Barrett's esophagus have reduced sensation of acid reflux events and therefore may be unaware of ongoing reflux. On once-daily PPI therapy, abnormal distal esophageal acid exposure was detected in 40–60% of asymptomatic patients with Barrett's esophagus (107–109). Even on higher doses of omeprazole of

40 mg b.i.d., as many as 24% of Barrett's patients were shown to have abnormal total or supine distal esophageal acid exposure values (110). Titration of PPI dosing based on normalization of acid exposure by pH monitoring in patients with Barrett's esophagus has been proposed but the benefit of such an approach is as yet unproven (111). Furthermore, whether such paradigms should be extended to patients with other reflux complications such as peptic strictures is unknown and currently not recommended. Similarly, it is generally not recommended that pH monitoring be routinely performed in asymptomatic patients who have undergone endoscopic therapy or antireflux surgery for complications that resulted from GERD.

REFRACTORY HEARTBURN. One of the most common uses of pH monitoring is in the evaluation of patients with persistent symptoms of reflux despite medical or surgical therapy. In the assessment of such patients, reflux monitoring by pH, bile acid reflux detection, or impedance monitoring attempts to discern whether ongoing symptoms are the result of incompletely treated GERD or an etiology unrelated to GERD. Endoscopic detection of distal erosive esophagitis while fairly specific is not a very sensitive test in this scenario. Empiric medical treatment as a therapeutic trial is appropriate in some circumstances such as in patients with continued heartburn following fundoplication but the converse, surgical therapy in patients failing medical therapy, is precarious in light of the reduced likelihood of GERD in such patients as well as risks inherent to surgery.

Refractory heartburn can be defined as the presence of heartburn that does not respond to therapy with acid-suppressing medications. While PPI therapy would generally be accepted as the best therapeutic agent in this regard, the dosing and timing of PPI therapies to define treatment failure are not established. While once-daily PPI therapy controls symptoms and heals esophagitis in over 90% of patients, data on the normalization of esophageal acid exposure are limited, as pH testing is not an end point of most clinical trials. Limited prospective studies have demonstrated normalization of esophageal pH with q.d. PPI therapy in over 90% of patients with typical reflux symptoms (60, 112, 113). On the other hand, patients with more severe degrees of erosive esophagitis have significantly greater abnormal esophageal acid exposure in spite of PPI therapy (114, 115). Retrospective studies have reported a range of abnormal esophageal acid exposure values that depend upon the indication for the study as well as PPI dosing schedule. Katzka *et al.* reported abnormal esophageal pH studies in 56% of patients with refractory heartburn and 28% of patients with atypical reflux symptoms while taking omeprazole 20 mg b.i.d. and using the stricter definition of normal as esophageal pH <4 of 1.6% (116). In a larger study using a threshold abnormal esophageal pH exposure of >5.5% (28), Charbel reported that 30% of patients with either typical or extraesophageal symptoms had abnormal pH monitoring on q.d. PPI therapy. These proportions

fell to 7% for the typical and 1% for the extraesophageal patients taking b.i.d. PPI therapy. As both studies were retrospective chart reviews, many patients had been referred for ongoing symptoms despite therapy. These findings allude to a limited role for esophageal pH monitoring in patients failing b.i.d. PPI therapy, especially in those with extraesophageal symptoms. A different conclusion can be reached from the data by Milkes *et al.* who prospectively studied a cohort of VA patients with GERD but without Barrett's esophagus who were asymptomatic on PPI therapy (40). A surprising 50% of these patients had abnormal esophageal pH studies, with three-quarters taking b.i.d. PPI therapy.

Reconciling these disparate data, three general observations can be made regarding the utility of pH testing on-therapy for patients presenting with refractory reflux symptoms. First, ongoing abnormal esophageal acid exposure frequently occurs in patients with refractory typical or atypical reflux symptoms taking once-daily PPI therapy. Second, patients with more severe complications of reflux that include higher grades of esophagitis and Barrett's esophagus have substantially lower rates of pH normalization, even on b.i.d. PPI therapy. And third, the diagnostic yield for pH testing for refractory patients presenting with typical reflux symptoms is greater than that for patients presenting with extraesophageal symptoms. This last observation likely reflects the lower background prevalence of GERD in patients presenting with extraesophageal symptoms.

pH testing of patients with refractory reflux symptoms is most commonly done with the patient taking PPI therapy, usually at b.i.d. dosing. A negative study after a trial of drug therapy provides convincing evidence that the patient's symptoms should not be attributed to ongoing acid reflux. Inclusion of a symptom-reflux correlation measure helps in excluding the possibility of esophageal acid hypersensitivity. A negative pH study on-therapy, however, does not exclude the possibility of underlying reflux that may be a cofactor in a patient's presentation and is being adequately suppressed by the PPI. Furthermore, adequate acid suppression may mask the detection of nonacid reflux events. The use of the wireless pH system for 4-day recordings allows for combined testing both off and on PPI therapy and may circumvent certain limitations of on-therapy testing (19). While both bile acid reflux monitoring and esophageal impedance are very promising technologies, further studies are needed to determine their role in patients with refractory reflux. Impedance is superior to pH monitoring in the detection of reflux symptoms associated with weakly acidic or nonacid reflux that persists on PPI therapy, especially regurgitation. However, the clinical importance of nonacid regurgitation is uncertain and patients' self-reporting of symptoms of regurgitation may or may not necessitate objective verification. Studies from patients with typical reflux symptoms have demonstrated that the minority of perceived reflux events are attributable to weakly acid reflux (92). Studies examining the clinical outcomes of patients refractory to PPI therapy whose symptoms are attributed to nonacid reflux are needed before either impedance or bile acid

reflux monitoring are recommended for widespread clinical use.

In the case of postfundoplication patients, patients may present with ongoing symptoms on the basis of a failed procedure or initial misdiagnosis of GERD as the basis of the symptoms. Further complicating the evaluation, some postfundoplication patients present with dyspeptic symptoms that are recognized consequences of an adequate procedure (gas bloat syndrome) but may be confused with GERD. Appropriate and careful patient selection with judicious use of preoperative reflux testing combined with a high success rate for fundoplication makes the need for postoperative reflux testing uncommon. pH monitoring is appropriate in the evaluation of postfundoplication patients with reflux symptoms who have not responded to empiric trials of PPI therapy. Dysphagia, abdominal or chest pain, or dyspeptic symptoms in postfundoplication patients are generally best evaluated with barium studies, endoscopy, and esophageal manometry.

CHEST PAIN. Up to 30% of patients with recurrent chest pain have normal coronary arteriograms. Chest pain related to GERD may mimic angina pectoris. In published series, up to 60% of patients with noncardiac chest pain (NCCP) have abnormal esophageal pH studies, whether defined by abnormal acid exposure times and/or symptom-reflux association (117). However, the majority of these patients have typical reflux symptoms and it is unclear whether or not ambulatory esophageal pH monitoring detects additional cases of acid-related chest pain not identified by history or endoscopic examination.

Empirical testing with high-dose PPIs appears to be the investigation of choice for the diagnosis of GERD in patients with NCCP (118–120). It is simple, noninvasive, cost-effective, and suggests causality, although a placebo response is possible. Ambulatory pH monitoring potentially may be helpful in patients who have not responded to high-dose PPIs. The study should be performed on PPI therapy and patients encouraged to have a normal active day so as to hopefully replicate their symptoms. False-negative tests may occur if patients do not perform routine activities or eat less than usual. In this regard, the wireless pH capsule with its improved tolerability may have distinct advantages over catheter-based pH recording. Some investigators have noted that off-therapy pH testing may also have utility by significantly increasing the likelihood of a positive reflux symptom association (31). Whether done off or on therapy, the patient with frequent chest pain episodes and normal pH testing confidently excludes acid reflux as the cause of NCCP. Analysis of pH data on patients with both chest pain symptoms and persistent reflux events on PPI therapy should incorporate a symptom-reflux correlation measure such as the SI, SSI, or SAP. However, application of pH testing remains untested in any large, prospective, controlled clinical trial. Likewise, the role of impedance and bile acid reflux monitoring has not been evaluated in NCCP patients.

Extraesophageal Manifestations of GERD

CHRONIC LARYNGEAL SYMPTOMS. Patients with predominantly laryngeal symptoms such as chronic cough, sore throat, hoarseness, globus, and excessive throat clearing are often diagnosed with GERD after laryngoscopy. However, the laryngeal examination may not be a specific marker for acid reflux disease (121). Twenty-four-hour pH monitoring is often the next test employed as endoscopy infrequently shows esophagitis. The overall pretherapy prevalence of an abnormal pH test in this population is reported to be 53% with the prevalence of excessive distal, proximal, and hypopharyngeal acid exposure being 42%, 44%, and 38%, respectively (122). While these studies suggest abnormal reflux events may be present in patients with throat symptoms, it does not establish causality. This was shown convincingly in a recent placebo-controlled study of 145 patients with suspected reflux-related ENT symptoms and signs treated with high-dose esomeprazole or placebo for 16 wk (123). The degree of symptomatic or laryngeal involvement was independent of pretherapy pH results and neither the presence of esophageal or hypopharyngeal acid reflux predicted a favorable response to PPI therapy.

Some suggest that pharyngeal acid reflux might better identify patients with suspected ENT symptoms from GERD. However, probe positioning is highly operator-dependent and variable (direct visualization by laryngoscopy *versus* measurement by manometry), artifacts are common, therefore, the computer interpretations need to be reviewed manually (70), the range of normals is poorly defined (none to 4 pH drops <4) (124–126), and 10–30% of healthy volunteers meet published criteria for abnormal pharyngeal reflux, suggesting some reflux into the hypopharynx may be a normal phenomenon (127). Even applying less restrictive pH criteria (*i.e.*, pH drop of 1.0 or 1.5 units rather than 2.0 units) does not help discriminate healthy volunteers and patients with suspected reflux-related ENT complaints (128). Finally, and most clinically relevant, several studies found that positive results of pharyngeal testing do not predict a more favorable response to antireflux therapy (124, 129). For example, Ulualp *et al.* (129) reported that the degree of symptom improvement in 19 of 27 patients exhibiting pharyngeal reflux episodes was similar to the remaining eight patients not having pharyngeal reflux.

The accumulating data seriously question the clinical usefulness of esophageal or hypopharyngeal pH monitoring in the initial evaluation of patients with suspected acid-related ENT complaints. As with NCCP, the practical and popular approach is an empiric trial with a b.i.d. PPI regimen for several months, reserving pH testing for patients with persistent symptoms (121). However, here again, the results of acid pH testing have limited clinical utility. Among 115 patients who continued to have extraesophageal symptoms while on b.i.d. therapy, Charbel *et al.* (39) found that only 1% had persistent abnormal acid reflux values.

Studies using impedance pH monitoring in patients with extraesophageal symptoms unresponsive to PPI therapy show little evidence of nonacid reflux, except in the chronic cough

patient. In a study of 22 patients with chronic cough, Sifrim *et al.* (130) found that combining ambulatory manometry with impedance-pH identified an additional five patients (23%) where the symptom association was positive for weakly acidic acid reflux. Weakly alkaline reflux was very rare and there were no patients with a positive symptom association for this type of reflux. Further studies are needed to determine if pH testing alone is capable of detecting weakly acidic reflux events without concomitant impedance monitoring. Whether this subset of patients with cough associated with nonacid reflux in the form of weakly acidic reflux will respond to high-dose PPI therapy, baclofen therapy, or antireflux surgery is unknown at this time.

ASTHMA. The prevalence of GERD in asthmatics is reported to be between 34% and 89% (131). Estimates vary greatly depending on the group of patients studied and how acid reflux is defined (*e.g.*, symptoms or 24-h pH monitoring), being highest in specialized centers dealing with complicated asthmatics and studies defining disease by pH testing. Abnormal acid reflux values may be as common in asthmatics without reflux symptoms (“silent refluxers”) as those with chronic heartburn complaints (132).

The role of esophageal pH monitoring is poorly defined in asthma patients. Although a recent literature review (122) found the overall prevalence of abnormal pH tests to be 66%, this test does not define whether the acid reflux is causing the asthma, or the GERD is induced during asthma attacks produced by decreasing intrathoracic pressure. Several authors have attempted to use esophageal pH monitoring to assess treatment outcomes, however, results are inconsistent. For example, Kiljander *et al.* (133) used dual pH monitoring to assess the effect of omeprazole on asthma symptoms. Of the 107 patients tested, 57% had abnormal pH values, but only 35% reported improvement of their asthma symptoms on therapy with little improvement in pulmonary function. In contrast, Harding *et al.* (134) found pH monitoring, especially in the proximal esophagus, to be a useful clinical indicator of treatment response. In this study, 30 patients with asthma and GERD were treated with omeprazole (20 mg), with titration of the dose until acid suppression was confirmed by pH testing. They found that 22 patients (73%) responded to therapy as shown by improvement in asthma symptoms or peak expiratory flow rates. Abnormal proximal reflux (pH <4 greater than 1.1%) predicted asthma response to PPIs with 100% sensitivity, 44% specificity, 79% positive predictive value, and 100% negative predictive value. Unfortunately, other studies have not confirmed this observation.

As with other extraesophageal symptoms, most patients with GERD-suspected asthma do not initially require esophageal pH testing. Rather, empiric acid reflux suppression with double-dose PPI followed by 24-h pH monitoring on drug in nonresponders is the most cost-effective means of determining if GERD is worsening a patient’s asthma (135). Treatment studies have demonstrated greater effectiveness of antireflux surgery when compared in an uncontrolled manner

to separate reports of medical therapy for GERD. While this observation may reflect differences in study design between medical and surgical trials, it does raise the possibility that nonacid reflux has a role in asthma. Studies looking at impedance monitoring in asthma are awaited.

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APPENDIX

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.
