Donald O. Castell, M.D., Series Editor

Diagnosis of GERD: Multichannel Intraluminal Impedance

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INTRODUCTION

Multichannel intraluminal impedance (MII) is a relatively new technology that allows detection of bolus movement within the esophagus without the use of radiating energy. First described by Silny in 1991 (1), over the years this technology was continuously developed and adapted for daily clinical use. Combined with manometry (MII-EM) it provides a more detailed insight of the relationship between esophageal contraction and bolus movement (2). Combined with pH (MII-pH) it expands the ability to detect all types of gastroesophageal reflux episodes and categorize them by their chemical (acid, non-acid) and physical (liquid, gas, mixed) properties (3).

PRINCIPLES OF MULTICHANNEL INTRALUMINAL IMPEDANCE

Multichannel intraluminal impedance testing is based on measuring changes in electrical conductivity of intraluminal content as boluses move through the esophagus. In direct current (DC) circuits the inverse of electrical conductivity is electrical resistance. In alternating current (AC) circuits the resistance to electrical current flow is called impedance (electrical symbol "Z"). The basic component of this method is the impedance circuit (Figure 1). Two metal (steel) rings separated by an isolator (i.e. silicon catheter) are connected to an alternating current (AC) generator. The poor electrical conductivity of the silicon catheter doesn't allow the current to flow between the two rings unless it is carried by electrical charges surrounding the isolator.

Suspended in air the impedance catheter records very high impedance values. When inserted in the esophagus, the small number of ions located in the esophageal mucosa will close the impedance circuit and the impedance circuit will measure relatively stable impedance baselines around 1500–2000 Ohm. When a liquid bolus enters the impedance-measuring segment between the two rings, the ions in the bolus increase electrical conductivity and thereby decreasing electrical impedance (Figure 2).

Bolus entry and exit points are determined in reference to the 3-second average impedance prior to the drop in impedance (baseline) and the lowest impedance value recorded during bolus presence (nadir). Since the change in impedance is very rapid, by convention,

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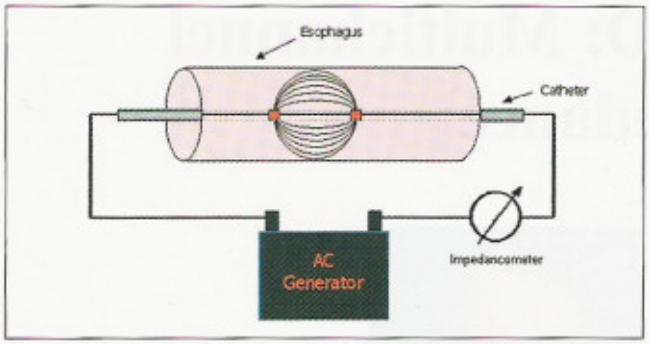

Figure 1. Schematic representation of the intraesophageal impedance circuit. Two metal rings on a catheter are attached to an AC generator. The electric circuit is closed by the electric charges (ions) within the lumen between the two metal rings.

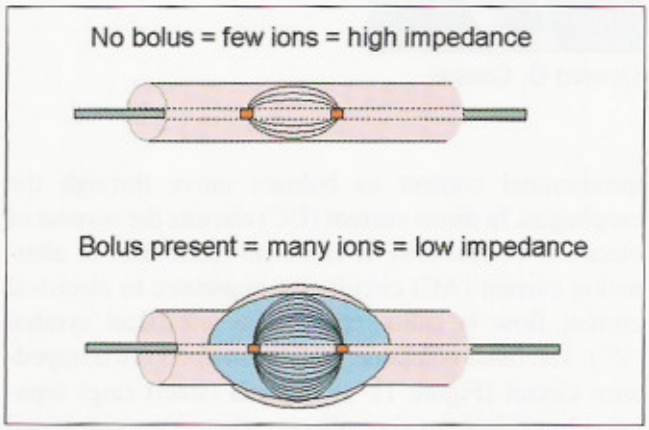

Figure 2. Changes in intraluminal impedance are determined by an increased number of ions during bolus presence.

bolus entry is considered to occur at the 50% drop in impedance from baseline to the nadir (Figure 3). Also, by convention, bolus exit is declared when the impedance returns from nadir to the 50% point that determined bolus entry. Small amounts of air, traveling ahead of the bolus produce a rapid rise in impedance but, by convention, only the liquid component of the bolus is used when determining bolus entry and exit (4).

While bolus presence in the esophagus can be detected by a single impedance-measuring segment, multiple impedance measuring segments on the same catheter are required to determine the direction of bolus movement. The timing of bolus entry at various levels in the esophagus can identify antegrade from retrograde bolus movement. Bolus entering the proxi-

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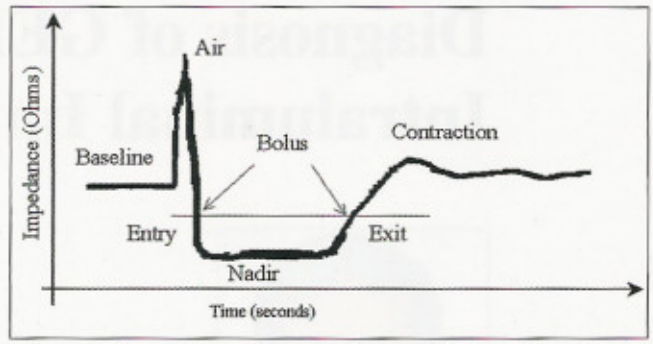

Figure 3. Impedance changes observed during bolus transit over a single pair of measurement rings separated by 2 cm. A rapid raise in resistance is noted when air traveling in front of the bolus head reaches the impedance measuring segment followed by a drop in impedance once higher conductive bolus material passes the measuring site. Bolus entry is considered at the 50% drop in impedance from baseline relative to nadir and bolus exit at the 50% recovery point from nadir to baseline. Lumen narrowing produced by the contraction transiently increases the impedance above baseline.

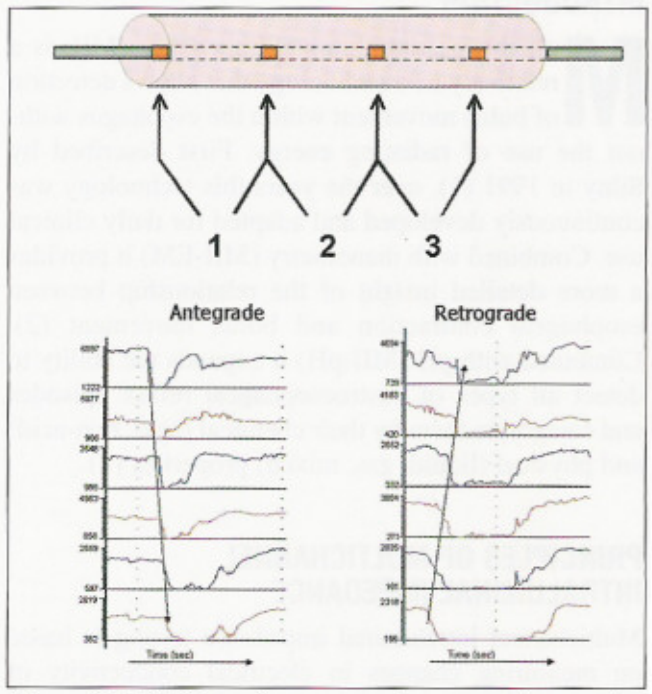

Figure 4. Multiple impedance measuring segments mounted on the same catheter allow determination of the direction of bolus movement. Decrease in impedance starting proximal and progressing distally indicated antegrade bolus movement (i.e. swallowing). Decrease in impedance starting distally and progressing proximally indicates retrograde bolus movement (i.e. reflux).

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mal segment and progressing distally indicates antegrade bolus movement as seen in swallowing while bolus entering first the distal segment and then advancing proximally indicates retrograde bolus movement as seen during reflux episodes (Figure 4).

Using these principles, impedance measuring rings can be mounted on conventional manometry catheters (combined MII-EM) allowing simultaneous determination of bolus movement and intraesophageal pressures or mounted on pH catheters (combined MII-pH) allowing detection of reflux episodes independent of the H+ concentration (i.e. pH values).

COMBINED MULTICHANNEL INTRALUMINAL IMPEDANCE AND MANOMETRY (MII-EM)

Before esophageal pH testing became available for clinical use in the mid 1970's (5), esophageal manometry was used to support the diagnosis of gastroesophageal reflux disease (GERD). Identifying low lower esophageal sphincter (LES) pressures or decreased esophageal contraction amplitudes were considered findings supporting the concepts of impaired LES barrier and poor esophageal clearance as part of esophageal motility abnormalities associated with GERD (6). Subsequent combined video-fluoroscopy and manometry studies reported that, even though poor esophageal clearance was associated with an increased number of manometric ineffective swallows (i.e. contraction amplitude less than 30 mmHg), not all manometric ineffective swallows lead to incomplete bolus transit (7).

Similar to the study by Kahrilas, et al (7) studies using combined MII-EM in both healthy volunteers (2) and patients with IEM (8) found that some swallows with contraction amplitude less than 30 mmHg in the distal esophagus (manometric ineffective swallows) have incomplete bolus transit while other manometric ineffective swallows have complete bolus transit (Figure 5). Factors influencing whether manometric ineffective swallows have complete bolus transit include the distal esophageal amplitude (average amplitude at two distal esophageal sites) and a number of sites with amplitudes less than 30 mmHg. Also, studies in a large group of patients with esophageal motility abnormalities found that almost all patients with normal esophageal manometry, nutcracker esophagus and isolated LES abnormalities have normal bolus transit while approximately half of patients with manometric defined ineffective esophageal motility (IEM) and distal esophageal spasm (DES) have abnormal bolus transit(9). While GERD is commonly associated with IEM and occasionally with DES, these data invite further investigation of the role of abnormal bolus transit in patients with GERD.

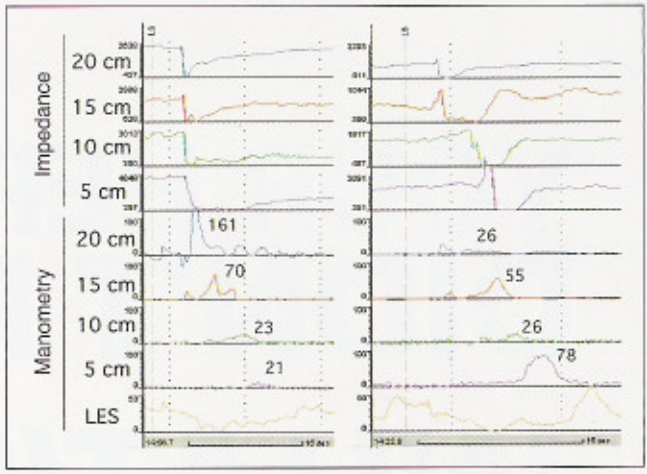

Figure 5. Combined manometry-impedance tracings showing examples of manometric ineffective swallows with incomplete (A) and complete (B) bolus transit.

Recently Pandolfino and colleagues adapted combined multichannel intraluminal impedance and manometry to evaluate LES opening and bolus movement during deglutitive and transient lower esophageal sphincter relaxations (tLESRs) (10). This technique has the potential of advancing the knowledge not only in understanding bolus transit during reflux but also to evaluate the characteristics of reflux episodes that trigger esophageal peristalsis and clearance of gastroesophageal refluxate by primary and secondary peristalsis.

COMBINED MULTICHANNEL INTRALUMINAL IMPEDANCE AND PH (MII-PH)

Since first described by Spencer in 1969 (11), many investigators have adopted intraesophageal pH testing as the gold standard for diagnosing GERD. Current criteria rely on a rapid decline in intraesophageal pH as

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a marker for gastric content being present in the esophagus. Therefore, conventional pH testing is limited in detecting gastroesophageal reflux episodes during which the pH fails to fall below this threshold. Combined MII-pH represents a shift in the reflux-testing paradigm. MII detects all types of GER episodes by retrograde progressing changes in intraluminal impedance as the reflux episode advances from the stomach into the esophagus. The information from the pH electrode is used only to characterize the H+ concentration of the GER episodes and separate them into acid or non-acid by pre-established criteria.

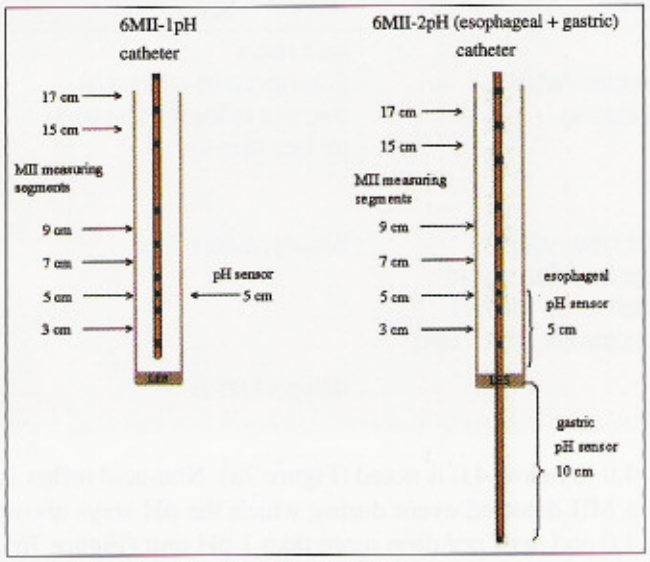

Figure 6. Combined MII-pH catheters.

The ability of combined MII-pH to detect and characterize non-acid GER represents an important advance for clinical testing of non-acid reflux (12). Previously other techniques were developed in order to overcome the limitations of conventional pH testing in detecting GER episodes during which the pH is not below 4.

Bilirubin monitoring (Bilitec®) requires the presence of bilirubin in the gastroesophageal refluxate in order to detect the presence of non-acid material in the esophagus (13). Studies involving simultaneous MII and bilirubin monitoring suggest that only 10% of non-acid reflux episodes contain bile (14). After ingestion of a radio-labeled meal, scintigraphy can also detect GER independent of the pH of the refluxate, although this technique is limited due to the continious emptying of the tracer from the stomach and the use of radi-

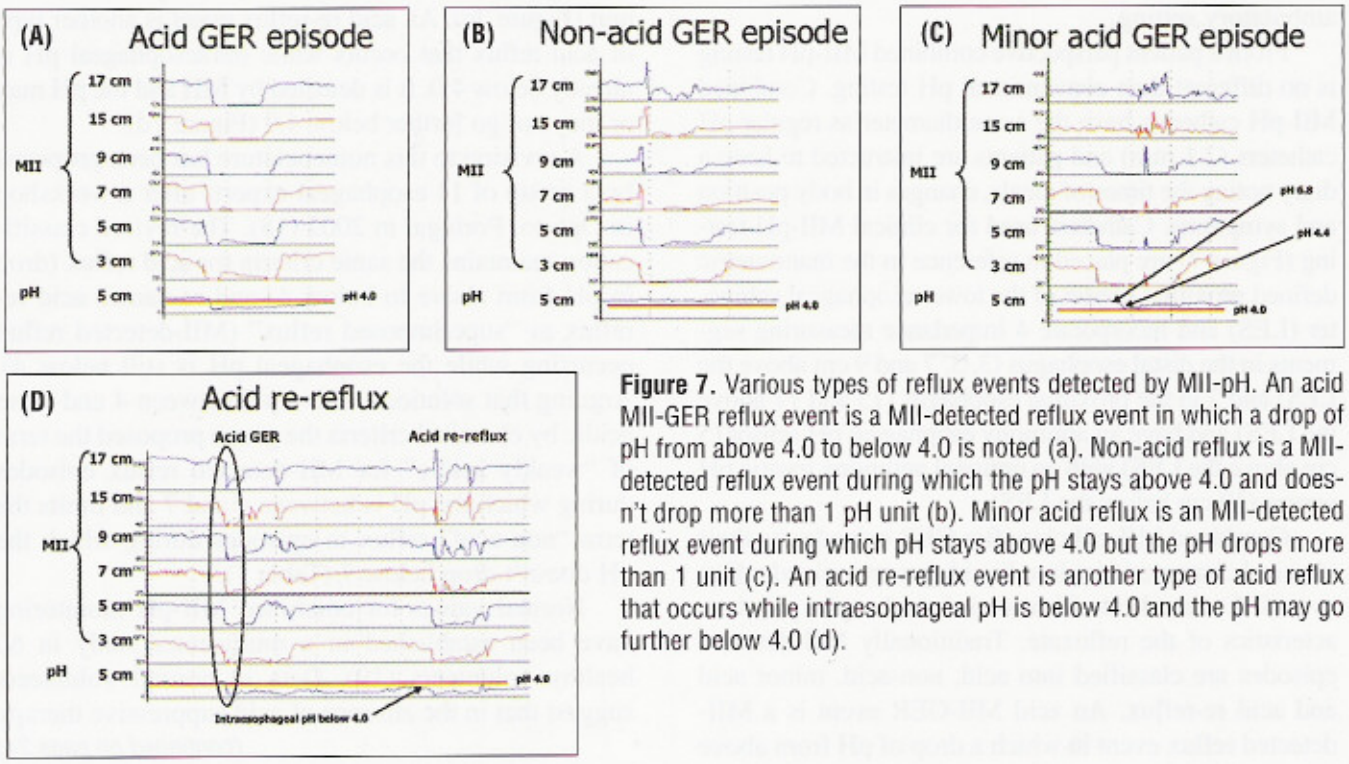

Figure 7. Various types of reflux events detected by MII-pH. An acid MII-GER reflux event is a MII-detected reflux event in which a drop of pH from above 4.0 to below 4.0 is noted (a). Non-acid reflux is a MII-detected reflux event during which the pH stays above 4.0 and doesn't drop more than 1 pH unit (b). Minor acid reflux is an MII-detected reflux event during which pH stays above 4.0 but the pH drops more than 1 unit (c). An acid re-reflux event is another type of acid reflux that occurs while intraesophageal pH is below 4.0 and the pH may go further below 4.0 (d).

Table 1
Traditional and revised classification of GER episodes

	pH monitoring	*MII-pH monitoring*	
pH		*Traditional classification*	*Revised classification (Oporto Group 2002)*
Less than 4	Acid reflux	Acid reflux Acid re-reflux (MII detected reflux starting while pH less than 4)	Acid reflux Superimposed reflux (MII detected reflux starting while pH less than 4)
Between 4 and 7	No reflux	Non-acid (MII detected reflux with pH above 4 and pH change less than 1 unit) Minor-acid (MII detected reflux with pH above 4 and pH change greater than 1 unit)	Weakly acidic reflux
Greater than 7			Non-acid reflux

ation (15,16). Another method of detecting gastroesophageal reflux independent of the chemical composition could be manometric monitoring with identification of tLESRs and common cavity events (17) although this method has not been validated in the ambulatory setting.

From a patient perspective combined MII-pH testing is no different than conventional pH testing. Combined MII-pH catheters have the same diameter as regular pH catheters (2.1 mm) and patients are instructed to keep a diary noting the times of meals, changes in body position and symptoms. Catheters used for clinical MII-pH testing (Figure 7) are placed in reference to the manometric defined proximal border of the lower esophageal sphincter (LES) and incorporate 4 impedance measuring segments in the distal esophagus (3, 5, 7 and 9 cm above the LES) and 2 in the proximal esophagus (15 and 17 above the LES) and have an antimony esophageal pH sensor (5 cm above the LES) with an optional antimony gastric pH sensor (10 cm below the LES).

Combined MII-pH classifies GER episodes by their physical characteristics into liquid, gas and mixed reflux events. A second classification is based on the pH characteristics of the refluxate. Traditionally MII-detected episodes are classified into acid, non-acid, minor acid and acid re-reflux. An acid MII-GER event is a MII-detected reflux event in which a drop of pH from above 4.0 to below 4.0 is noted (Figure 7a). Non-acid reflux i a MII-detected event during which the pH stays abov 4.0 and does not drop more than 1 pH unit (Figure 7b) Minor acid reflux is a MII-detected reflux event durin which pH stays above 4.0 but the pH drops more than unit (Figure 7c). An acid re-reflux event is another typ of acid reflux that occurs while intraesophageal pH i already below 4.0. It is detected by MII and the pH ma or may not go further below 4.0 (Figure 7d).

A revision to this nomenclature has been proposed by a group of 11 esophageal experts after a worksho in Oporto, Portugal in 2002 (18). The revised classifi cation maintains the same criteria for acid reflux (dro in pH from above to below 4) and re-names acid re reflux as "superimposed reflux" (MII-detected reflu occurring while the esophageal pH is still below 4) Arguing that solutions with a pH between 4 and 7 ar acidic by chemical criteria the group proposed the ter of "weakly acidic" for MII-detected reflux episode during which the pH is between 4 and 7 and limits th term "non-acid" reflux to episodes during which th pH doesn't drop below 7 (Table 1).

Normal values for combined MII-pH monitorin have been established in a multicenter study in 6 healthy volunteers (19). Data in normal volunteer suggest that in the absence of acid suppressive therapy

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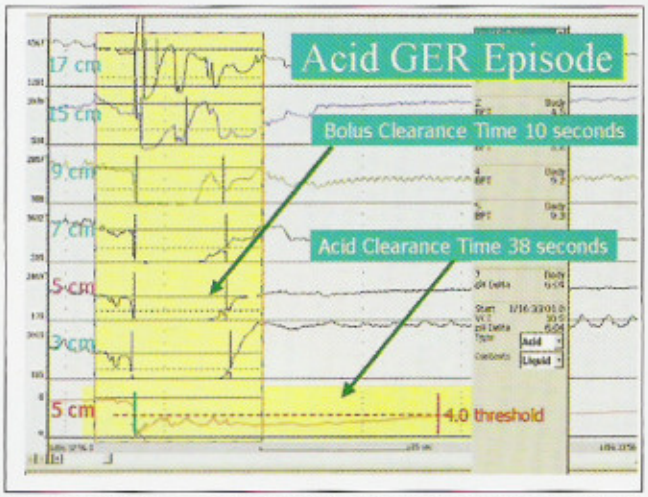

Figure 8. Differences in (acid) bolus clearance time and acid clearance time (i.e. the time required for the pH to recover to above 4).

the vast majority of GER episodes are acidic, with non-acid GER episodes limited primarily to post-prandial periods. Of particular interest in this study is the observation that the time intraesophageal pH is below 4 (detected by pH) is much longer compared to the actual acid bolus presence time (detected by impedance) underscoring the observation that acid clearance requires not only removal of the bolus but also neutralization of the mucosal acid (Figure 8). These data confirm prior scintigraphic-pH data by Helm, et al (20) that demonstrated that esophageal acid clearance time (assessed by pH) was much longer compared to the time the radiolabeled HCl bolus was present in the esophagus.

Probably the most important role of combined MII-pH monitoring is in the evaluation of adult patients with residual symptoms on acid suppressive therapy and in infants (Table 2). The interest for non-acid GER testing in infants comes from the facts that the acid output is decreased compared with adults and the feeding patterns (drinking milk or formula every 2–3 hours) maintain long periods of time with the stomach full and with buffering of intragastric acid concentrations (21,22).

Given the high prevalence of GERD symptoms (23) and the popularity of empiric PPI trials ("omeprazole test") to diagnose GERD (24,5) many patients present with persistent reflux symptoms on PPI therapy. In a large series (over 5000 patients) up to 40% of patients with GERD were having persistent symptoms after 4 weeks of PPI therapy (26). Studies from our laboratory have suggested that continuing symptoms on acid suppressive therapy are associated with both acid and non-acid GER episodes or not related to reflux episodes (27).

Table 2
Clinical indications for combined MII-pH testing

- Patients with persistent symptoms on acid suppressive therapy
- Patients with reflux symptoms and achorhidria (i.e. atrophic gastritis)
- Patients with reflux symptoms after surgical gastrectomy
- Patients with primarily post-prandial symptoms
- Patients with reflux symptoms and frequent meal ingestion (i.e. infants)

Preliminary data from a multicenter study evaluating the relationship between residual symptoms on PPI therapy and acid and non-acid reflux suggest that persistent acid reflux is associated with symptoms in only 20% of patients on PPI therapy (28). In approximately 40% of patients, the residual symptoms are due to non-acid reflux while in the remaining 40% of patients the symptoms are not related to GER episodes. These percentages are dependent on the type of (typical or atypical) GERD symptoms.

SUMMARY

Combined MII-pH monitoring is an important addition to the clinical armamentarium for diagnosing and managing GERD. Since GER episodes are detected independent of their pH combined MII-pH allows detection of all types of reflux events providing information not only about their chemical (pH) composition but also about their physical properties (liquid, gas, mixed). By its ability to separate bolus clearance from acid clearance and identify acid re-reflux episodes combined MII-pH improves our understanding regarding the mechanisms of long pH-detected acid reflux episodes.

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The most important addition is the ability to identify the mechanism of residual GERD symptoms on acid suppressive therapy as due to persistent acid reflux, non-acid reflux or no reflux. In our experience, combined MII-pH has revised the diagnostic algorithm for GERD (Figure 9). ■

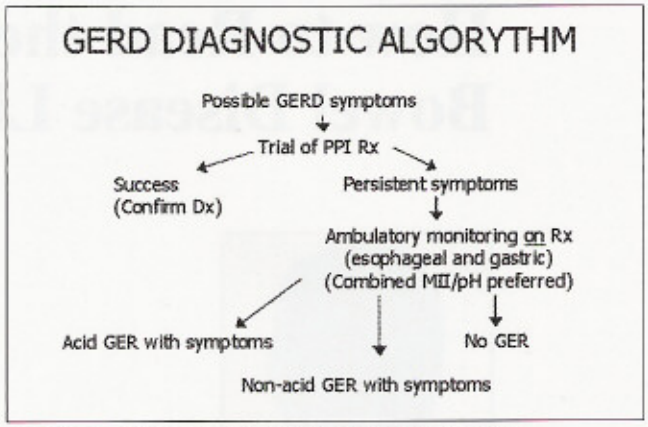

Figure 9. Revised diagnostic algorithm for GERD.

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