Majority of symptoms in esophageal reflux PPI non-responders are not related to reflux

S. ROMAN,* † L. KEEFER, * H. IMAM,* ‡ P. KORRAPATI,* B. MOGNI,* K. EIDENT,* L. FRIESEN,* P. J. KAHRLAS,* Z. MARTINOVICH* & J. E. PANDOLFINO*

*Division of Gastroenterology and Hepatology, Department of Medicine, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA
†Digestive Physiology, Hospices Civils de Lyon, Lyon I university and LabTAU Inserm 1032, Lyon, France
‡Gastroenterology and Hepatology Unit, Department of Internal Medicine, Assiut University Hospital, Assiut, Egypt

Key Messages
• The heterogeneity of PPI non-responder profiles might explain the failure of reflux inhibitors and the treatment of these patients should be focused on mechanisms beyond reflux.
• The goal of our study was to determine reflux patterns on 24-h pH-impedance monitoring performed on PPI and to correlate impedance patterns and symptom occurrence in PPI non-responders.
• Reflux impedance patterns were characterized on 24-h pH-impedance monitoring performed on PPI in 78 PPI non-responder patients. Association between reflux impedance patterns and symptom occurrence was studied.
• The impedance reflux profile in PPI non-responders was heterogeneous and the majority of the reflux events were not associated with symptoms.

Abstract
Background Genesis of persistent gastro-esophageal reflux symptoms despite proton pump inhibitor (PPI) therapy is not fully understood. We aimed at determining reflux patterns on 24-h pH-impedance monitoring performed on PPI and correlating impedance patterns and symptom occurrence in PPI non-responders. Methods Seventy-eight PPI non-responder patients underwent 24-h pH-impedance monitoring on PPI. Reflux impedance characterization included gastric and supragastric belches and proximal extent of reflux. Symptoms were considered associated with reflux if occurring within 5 min after a reflux event. Patients were classified into three groups: persistent acid reflux (acid esophageal exposure [AET] >5% of time), reflux sensitivity (AET <5%, symptom index [SI] ≥50%), and functional symptoms (AET <5%, SI <50%). Dominant impedance pattern was determined for each patient. Key Results Seven patients (9%) had persistent acid reflux, 28 (36%) reflux sensitivity, and 43 (55%) functional symptoms. A total of 4296 reflux events were identified (median per patient 45 [range 4–221]). Although liquid reflux was the most common pattern in all groups, patients with reflux sensitivity and functional symptoms had much more variability in their pattern profile with a large proportion being associated with gastric and supragastric belching. Only 417 reflux events (9.7%) were associated with symptoms. Reflux with a supragastric component and proximal extent were more likely to be associated with symptoms. Conclusions & Inferences The impedance reflux profile in PPI non-responders was heterogeneous and the majority of reflux events were not associated with symptoms. Thus, the treatment of PPI non-responders should focus on mechanisms beyond reflux, such as visceral hypersensitivity and hypervigilance.

Keywords gastro-esophageal reflux disease, pH-impedance monitoring, proton pump inhibitors, symptom.

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Neurogastroenterology & Motility [2015]

doi: 10.1111/nmo.12666

John E Pandolfino, MD, MS, Division of Gastroenterology/Hepatology, Department of Medicine, Feinberg School of Medicine, Northwestern University, 676 St Clair St, Suite 1400, Chicago, IL 60611-2951, USA.
Tel: +1 312-695-4513; fax: +1 312-695-3999;
e-mail: j-pandolfino@northwestern.edu
Received: 25 March 2015
Accepted for publication: 3 August 2015
INTRODUCTION

Gastro-esophageal reflux disease (GERD) symptoms are frequently encountered in Western countries; they affect around 20% of the population. Proton pump inhibitors (PPIs) are the mainstay of GERD treatment and they add substantial cost to the health care system.\(^1\) While the success rate for healing esophagitis is very high (80–90%),\(^2\) 20–60% of patients with GERD symptoms remain unsatisfied or symptomatic despite PPI therapy.\(^3\) Reasons for dissatisfaction and non-response are multiple: non-adherence to treatment, persistent esophageal acid exposure, reflux hypersensitivity, or esophageal hypervigilance. Understanding the mechanisms of PPI non-response in GERD is of importance to develop and offer the best therapeutic options to patients. It may also help to decrease health cost by decreasing unnecessary PPI use.

Esophageal reflux monitoring is helpful in determining the association between reflux events and symptom occurrence. Combined pH-impedance monitoring detects reflux events based on the presence of liquid and gas in the esophagus. These events are further characterized based on their pH as acid, weakly acidic, or weakly alkaline.\(^4\) While reflux events are physiological and encountered in asymptomatic controls, they tend to be more frequent,\(^5\) more likely acidic\(^6\), and more likely associated with symptoms\(^7\) in patients who report GERD symptoms.

Investigators have attempted to determine reflux characteristics that might be associated with symptoms perception. In a series of 1,807 reflux episodes identified in 32 patients who underwent 24-h esophageal pH-impedance monitoring off PPI, only 203 (11.2%) were symptomatic.\(^8\) Compared to non-symptomatic episodes, symptomatic reflux episodes had lower nadir pH, higher proximal extent, longer volume and acid clearance time, and were preceded by greater esophageal cumulative acid exposure. In a similar study performed in 20 patients with typical GERD symptoms despite double-dose PPI therapy, 1273 reflux episodes were identified and 312 (24.5%) were associated with symptoms.\(^9\) The only factor associated with perception was high proximal extent. Other studies suggested that reflux perception was enhanced by the presence of gas in the refluxate in patients with non-erosive reflux disease\(^10\) and in patients with poor response to acid suppressive therapy.\(^11\) This is consistent with the observation of Bravi et al. that air swallowing might be an important factor in PPI non-response.\(^12\) Among patients with typical GERD symptoms and abnormal esophageal acid exposure of PPI, the frequency of air swallowing was greater in the 26 patients who failed to respond to PPI therapy compared to the 18 patients who responded. Moreover, symptoms of PPI non-responders were more often preceded by mixed gas–liquid reflux events than those of PPI responders. Based on these observations, proximal extent of reflux and an air component may play a role in the persistence of GERD symptoms on PPI therapy.

Given the above data, we hypothesized that a more accurate description and categorization of reflux events may be helpful in explaining symptom correlation. We hypothesized that reflux patterns, including the direction of gas movement (belch vs supragastric belch), the timing between liquid and gas components (i.e., gas component preceding liquid component vs gas component within the liquid component), and proximal extent of the liquid component of the reflux might play roles in symptom genesis in patients who did not respond to PPI therapy. Hence, our goal was to describe detailed reflux patterns with ambulatory pH-impedance monitoring on PPI therapy and to determine whether these patterns influence symptom generation in PPI non-responders.

METHODS

Patients

We prospectively enrolled 78 consecutive PPI non-responder patients (28 males, mean age 51 years [range 19–76], mean body mass index [BMI] 29.3 kg/m\(^2\) [range 18.6–44.1]) who underwent 24-h pH-impedance monitoring on PPI from July 2011 to July 2014 at Northwestern University, Chicago, IL. The PPI non-response was defined as persistent GERD symptoms despite PPI treatment and the requirement for further evaluation using ambulatory reflux testing. Patients presented with various symptoms of GERD: heartburn, regurgitations, chest pain, cough, or sore throat. Patients with previous a history of scleroderma, esophageal surgery, or Barrett’s esophagus were excluded.

The study protocol was approved by the Northwestern University Institutional Review Board. All patients signed informed consent form.

Study protocol

High resolution manometry (HRM; ManoScan; Medtronic Inc, Minneapolis, MN, USA) was performed prior to 24-h pH-impedance monitoring (Sandhill Scientific, Inc, Highlands Ranch, CO, USA) to localize the esophagogastric junction (EGJ) and rule out major esophageal motility disorders. The pH-impedance catheter was positioned to measure esophageal pH, 5 cm above the proximal border of the EGJ and impedance 5, 5, 7, 9, 15, and 17 cm above the proximal border of the EGJ. Study was performed on PPI once daily in 25 patients and twice daily in 53 patients. Patients were encouraged to maintain their daily activities, sleep schedule, and eat meals at their normal times. They were also instructed to press the event marker button on the pH-impedance data logger whenever they experienced a symptom suggestive of reflux.
Symptoms and reflux in PPI non-responders

Data analysis

Clinical data and high resolution manometry Clinical data were obtained by searching patients' medical records and baseline questionnaire profile. Esophageal HRM were analyzed using Manoview software (Medtronic Inc). Esophagogastric junction end-expiratory pressure was measured in the absence of swallowing and esophageal motility disorders were diagnosed using the Chicago Classification version 3.0.13

*pH-impedance study* pH-impedance recordings were analyzed using dedicated software [Bioview Analysis®, version 5.5.5.1, Sandhill Scientific Inc.], Automated analysis was run fluid [Autoscan® function of Bioview Analysis® software] and tracings were then reviewed independently by two investigators (SR and HI). Disagreements were arbitrated by a third investigator (JEP).

Liquid reflux events were defined as a retrograde 50% drop in impedance starting distally at the level of the EGJ and propagating to at least the next two impedance channels. Only liquid reflux lasting more than 3 s were scored. Gas events were defined as a rapid [3000 ohms/s] increase in impedance to >5000 ohms, occurring simultaneously in at least two impedance channels. They were further subdivided into ‘gastric belch’ when a rapid increase in impedance moved from distal to proximal channels and ‘supragastric belch’ when a very rapid increase in impedance moved from proximal to distal followed by a retrograde decrease in impedance to baseline.14 Mixed liquid–gas events were defined as gas occurring immediately before or during a liquid reflux and were further subdivided into reflux starting with a gastric belch (when gastric belch preceded liquid component of the reflux), reflux induced by supragastric belch (when supragastric belch preceded liquid component of the reflux), reflux associated with gastric belch (when gastric belch occurred during the liquid component of the reflux), and reflux associated with supragastric belch (when supragastric belch occurred during the liquid component of the reflux). Liquid reflux events were considered swallow-induced if a swallow occurred immediately prior to the reflux event. Reflux events were considered to have reached the proximal esophagus when the liquid component of the reflux reached at least 15 cm above the EGJ. Thus, reflux events were classified as having one of six impedance patterns: gastric belch component (if reflux events with gastric belch component were the most frequent events), supragastric belch component (if reflux events with supragastric belch component were the most frequent events), swallow-induced reflux (if swallow-induced reflux events were the most frequent events), proximal reflux events (if proximal reflux events were the most frequent events), and ‘liquid reflux’ (if none of the above patterns was dominant).

Statistical analysis

Data are presented as percentage or median (range) and compared using chi-squared or Mann–Whitney tests. Dominant impedance pattern was determined for each patient and clinical and HRM characteristics of these dominant patterns were compared using chi-squared or Mann–Whitney tests. Hierarchical linear models were used to estimate the probability of symptoms within a time interval of 5 min following reflux events. Models evaluated alternative contrasts of the impedance patterns. In addition, the logistic relationship between the nadir pH and symptom probabilities was estimated.

RESULTS

Phenotypes of PPI non-responders

Among the 78 PPI non-responder patients included in this cohort, median AET was 0.5% (0.0–35.5) of total time and median number of reflux events (liquid, gas, or mixed) per patient was 45 (4–221). Seven patients (9%) had persistent acid reflux, 28 (36%) reflux-sensitive esophagus, and 43 (55%) functional symptoms. Characteristics of these groups are described in Table 1. While there was no difference in the detection of esophageal motility disorders among groups, reflux-sensitive patients had a more hypotensive EGJ than the others [8 mmHg [0–24] vs 11 [0–38], p = 0.02]. There was no difference between the patients on PPI once daily and those on PPI twice daily; in particular, distribution of persistent acid reflux, reflux-sensitive esophagus, and functional symptoms was similar.

Characterization of impedance patterns

A total of 4296 reflux events were identified. Reflux characteristics are presented in Fig. 1. Impedance patterns were distributed as follow: gastric belch 17.2%, supragastric belch 7.3%, liquid with gastric belch 15.4% (starting and associated with gastric belch 13.5% and 1.9%, respectively), liquid reflux with supragastric belch 11.0% (induced by and associated
with supragastric belch 8.6% and 2.4%, respectively), proximal liquid reflux 12.4%, swallow-induced liquid reflux 5.8%, and distal liquid reflux 30.9%.

Regarding the occurrence of impedance patterns per patient, all patients exhibited liquid events. Gastric belches were encountered in 92% of patients, supragastric belches in 56%, reflux starting with gastric belch in 91%, reflux induced by supragastric belch in 61%, reflux associated with gastric belch in 55%, reflux associated with supragastric belch in 47%. Swallow-induced liquid or mixed reflux events were noticed in 83% patients, and proximal (liquid or mixed) reflux events in 88%. The occurrence of these different patterns was similar in patients with persistent acid reflux, reflux-sensitive esophagus, and functional symptoms. The only exception was that patients with functional symptoms exhibited a less proximal reflux than the others (81% vs 97%, p = 0.03). Impedance patterns were similarly distributed in patients on PPI once and twice daily.

Distribution of dominant impedance patterns is presented in Table 2. Liquid reflux was the most frequent dominant pattern observed in our cohort. Patients with a dominant pattern of supragastric belching had lower BMI than patients with other dominant patterns (median BMI 23.6 [range 18.6–27.9] kg/m² vs 28.8 [18.8–44.1] p < 0.01). Ineffective esophageal motility was the most frequent motility disorder (41%) observed in patients with distal liquid reflux as a dominant pattern while HRM was most frequently normal in the other patterns (60%; p = 0.04).

**Reflex-symptom association**

A total of 1178 symptoms were reported with a median of 6 (0–159) symptoms reported per patient. Among the 4296 reflux events identified, only 417 (9.7%) were associated with symptoms. The median number of symptoms per patient and per hour was 0.3 (0.0–7.7) and the median number of symptoms associated with reflux event per hour was 0.1 (0.0–4.7). For the 66 patients who reported at least one symptom event, the SI was 42% (0–100). Patients with a dominant pattern of ‘supragastric belch component’ had higher SI than the others [85 [13–100] vs 40 [0–100], p = 0.02].

Based on hierarchical linear models analysis, the estimated probability that a reflux event was associated
with a symptom was 9.3% [95% confidence interval [CI] = 6.6–12.9). Proximal reflux events were more likely associated with symptoms than distal reflux events [12.7% [95% CI = 9.9–17.7] vs 7.8% [95% CI = 5.3–11.3], p = 0.001]. Reflux events with a supragastric belch component were more likely associated with symptoms than reflux with a gastric belch component [12.4% [95% CI = 7.8–19.2] vs 8.6% [95% CI = 6.2–12.0], p = 0.017]. Nadir pH was not significantly related to symptom probability (OR [95% CI] = 0.931 [0.839–1.034], p = 0.18). Table 3 reports the results of a model taking into account belch component, proximal extent, and swallow-induced events. Gastric belch alone, distal liquid reflux events alone, distal liquid reflux associated with gastric belch, and swallow-induced distal reflux were less likely associated with symptoms than proximal liquid reflux associated with supragastric belch or swallow-induced proximal liquid reflux.

**DISCUSSION**

The major finding of this study was that PPI non-responders have a heterogeneous profile on pH-impedance monitoring. Although liquid reflux events were the most frequent patterns in all three PPI non-responders subtypes [persistent acid reflux, sensitive esophagus, and functional symptoms], patients with sensitive esophagus and functional symptoms had much more variability in their impedance profile with a large proportion being associated with both sub- and supragastric belching. Furthermore, less than 10% of the reflux events were associated with symptoms and the majority of the symptoms recorded were not associated with reflux. Even if some reflux patterns tended to be more likely associated with symptoms, the association remained weak.

Our initial hypothesis that different impedance patterns might explain symptoms in PPI non-responders was not confirmed by these data. Rather, we observed heterogeneity in the impedance profiles and no profile that was clearly associated with subtypes of PPI non-responders. This finding might question the role of pH-impedance monitoring in PPI non-responders. Previous studies have also searched for predictive factors of response to PPI therapy based on pH-impedance criteria. In a series of 100 patients who underwent pH-impedance monitoring off PPI, Zerbib et al. failed to find any reflux characteristics that might predict response to PPI therapy. Patel et al.

### Table 2 Dominant impedance patterns in the three groups of proton pump inhibitors non-responders

<table>
<thead>
<tr>
<th>Dominant impedance pattern</th>
<th>Persistent acid reflux (n = 7)</th>
<th>Sensitive esophagus (n = 28)</th>
<th>Functional symptoms (n = 43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric belch component</td>
<td>1 (14%)</td>
<td>7 (25%)</td>
<td>13 (30%)</td>
</tr>
<tr>
<td>Gastric belch alone</td>
<td>1 (14%)</td>
<td>7 (25%)</td>
<td>8 (19%)</td>
</tr>
<tr>
<td>Liquid reflux starting with gastric belch</td>
<td>0</td>
<td>0</td>
<td>5 (12%)*</td>
</tr>
<tr>
<td>Supragastric belch component</td>
<td>0</td>
<td>5 (18%)</td>
<td>4 (9%)</td>
</tr>
<tr>
<td>Supragastric belch alone</td>
<td>0</td>
<td>2 (7%)</td>
<td>4 (9%)</td>
</tr>
<tr>
<td>Liquid reflux induced by supragastric belch</td>
<td>0</td>
<td>3 (11%)*</td>
<td>0</td>
</tr>
<tr>
<td>Swallow-induced reflux</td>
<td>0</td>
<td>1 (3.5%)</td>
<td>0</td>
</tr>
<tr>
<td>Proximal reflux</td>
<td>0</td>
<td>1 (3.5%)</td>
<td>3 (7%)</td>
</tr>
<tr>
<td>Liquid reflux</td>
<td>6 (86%)†</td>
<td>14 (50%)</td>
<td>23 (53%)</td>
</tr>
</tbody>
</table>

* p < 0.05 vs other groups; † p = 0.09 vs other groups.

### Table 3 Impedance patterns and probability of association with symptoms

<table>
<thead>
<tr>
<th>Pattern</th>
<th>Number of patients with this pattern</th>
<th>Number of events</th>
<th>Mean number of events per patient</th>
<th>Probability of association with symptom (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric belch (without liquid reflux)</td>
<td>72</td>
<td>738</td>
<td>10.3</td>
<td>7.5% (4.7–11.5)</td>
</tr>
<tr>
<td>Gastric belch with distal liquid reflux</td>
<td>70</td>
<td>583</td>
<td>8.3</td>
<td>7.7% (5.0–11.5)</td>
</tr>
<tr>
<td>Gastric belch with proximal liquid reflux</td>
<td>33</td>
<td>77</td>
<td>2.3</td>
<td>10.9% (5.4–20.9)</td>
</tr>
<tr>
<td>Supragastric belch (without liquid reflux)</td>
<td>45</td>
<td>312</td>
<td>6.9</td>
<td>10.6% (6.4–16.9)</td>
</tr>
<tr>
<td>Supragastric belch with distal liquid reflux</td>
<td>53</td>
<td>278</td>
<td>5.3</td>
<td>11.5% (6.8–18.6)</td>
</tr>
<tr>
<td>Supragastric belch with proximal liquid reflux</td>
<td>23</td>
<td>194</td>
<td>8.4</td>
<td>17.1% (10.8–25.9)*</td>
</tr>
<tr>
<td>Swallow-induced distal liquid reflux</td>
<td>58</td>
<td>212</td>
<td>3.7</td>
<td>8.8% (5.6–13.5)</td>
</tr>
<tr>
<td>Swallow-induced proximal reflux</td>
<td>21</td>
<td>38</td>
<td>1.8</td>
<td>20.3% (10.4–35.8)*</td>
</tr>
<tr>
<td>Distal liquid reflux (not swallow induced)</td>
<td>77</td>
<td>1330</td>
<td>17.3</td>
<td>8.2% (5.6–11.7)</td>
</tr>
<tr>
<td>Proximal liquid reflux (not swallow induced)</td>
<td>61</td>
<td>534</td>
<td>8.8</td>
<td>11.0% (7.3–11.1)</td>
</tr>
</tbody>
</table>

* p < 0.05 vs gastric belch, gastric belch with reflux, distal liquid reflux, swallow-induced distal reflux, and supragastric belch with distal liquid reflux.  
†p < 0.05 vs gastric belch, gastric belch with reflux, distal liquid reflux, swallow-induced distal reflux, and proximal liquid reflux.
demonstrated that the impedance profile did not predict response to PPI, but AET off PPI did predict response.\(^{17}\) Hence, the classical impedance parameters that include gas and liquid content and proximal extent have not been shown to be useful in predicting PPI response.

Our choice of using esophageal acid exposure rather than total number of reflux events is directly based on the study of Patel et al.\(^{17}\) as esophageal acid exposure was the only factor able to predict PPI response. Further we decided to consider the threshold of 5% for pathological esophageal acid exposure as the aim of PPI treatment is to relieve symptoms and also to ‘normalize’ esophageal acid exposure. We felt that using threshold established in healthy controls on PPI was somewhat artificial to define disease state.

In our study we chose, using a 5-min time frame, to evaluate the association between reflux and symptom instead of the common 2-min time frame. We acknowledge that a 2-min time frame is the optimal time to diagnose symptom-reflux association\(^{18}\) and using a longer time frame is a limitation of our study. Our purpose was to assess symptom mechanisms, and thus we decided to increase the sensitivity of this association by increasing the time frame to 5 min. Despite this longer time frame, a low proportion of reflux events were associated with symptoms in our series. This was previously noted by Tutuian et al. in a series of 120 patients who underwent pH-impedance monitoring on PPI using a 5-min frame for reflux-symptom association as us.\(^{11}\) They observed that mixed reflux and reflux with proximal extent were more likely associated with symptoms. Our results are consistent with those findings and provide a more detailed description of the type of gas-reflux pattern. The reflux events that were most likely symptomatic reached not only the proximal esophagus but were also associated with a supragastric component or were swallow-induced. The role of supragastric belches in the genesis of symptoms was reported in 90 patients who underwent 24-h impedance monitoring of PPI as part of the work-up for reflux symptoms.\(^{19}\) We demonstrated that this mechanism was also preponderant in PPI non-responders. Supragastric events and swallow-induced events share a common feature: both of them start with a swallow component. Thus, these events may or may not be induced voluntarily. They may also be secondary to sensitization or hypervigilance and are aimed at relieving some digestive tract discomfort.

Our results may have important clinical implications as the current paradigm is to treat all reflux events the same. Acidity is the primary target and PPIs are very effective in controlling acid exposure as evident by the low number of patients with abnormal acid exposure on PPI therapy. When PPIs fail to relieve symptoms, it has been proposed to target the number of reflux events as this should decrease reflux burden. However, our results suggest that there are major problems with this approach and that this could potentially explain why the improvement in symptom control with reflux inhibitors has been poor. For example, lesogabran, a gamma-aminobutyric acid (GABA)-B receptor agonist which reduces the frequency of transient lower esophageal sphincter relaxations, resulted in symptom relief in 16% of the patients who did not respond to PPI therapy vs 8% for placebo \(p = 0.03\) when used as PPI add-on therapy.\(^{20}\) Arbaclofen placarbil, a pro-drug of the GABA-B agonist baclofen, was not superior to placebo as add-on therapy in PPI non-responders.\(^{21}\) Due to the minimal [if any] efficacy of these drugs, most companies have abandoned their development. The heterogeneity we observed in our cohort of PPI non-responders may help explain the failure of these medications. None of the reflux inhibitors targeted a specific type of reflux and it is unlikely that any of these agents would preferentially reduce supragastric events or reduce proximal extent. On a purely numerical level, it is unlikely that reducing reflux event numbers would substantially reduce symptoms when only a small portion of reflux events are associated with symptoms. This approach would appear to be futile in PPI non-responders and treatment approaches should shift toward improving symptoms, as opposed to reducing reflux as there is little direct evidence to support a reflux-symptom correlation.

Our study has limitations. All patients were enrolled from a single center and sample size for each impedance pattern was limited. However, compared to previous studies, we included a substantial higher number of PPI non-responder patients. For example Bredenoord et al.\(^{8}\) and Zerbib et al.\(^{9}\) who examined the correlation between reflux patterns and symptoms occurrence reported on 32 and 20 patients, respectively. Another limitation of this study was the fact that we did not evaluate baseline impedance in our series as some data suggest this may help predict PPI response in patients with GERD symptoms. De Bortoli et al. showed that PPI response was associated with lower impedance baseline in patients with functional heartburn [negative endoscopy, negative AET, negative SI].\(^{22}\) Instead of searching for predictive factors of PPI response, we chose to focus on patients identified as PPI non-responders and search for specific impedance patterns associated with symptoms.

In conclusion, PPI non-responders have a heterogeneous reflux profile as determined by multichannel
intraluminal impedance monitoring. Most reflux events are not associated with symptoms and the type of reflux pattern was not predictive of symptom perception. This suggests that the target of treatment in PPI non-responders should be shifted to focus on altering sensitivity and reducing hypervigilance. Speech therapy might be also an option in patients with reflux with supragastric component. Escalation of antireflux therapy in this patient group should be approached cautiously as a reduction in reflux number may not be the appropriate therapeutic endpoint for patients not responding to PPI.

ACKNOWLEDGMENT
Guarantor of the article: John E Pandolfini, MD.

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FUNDING
This work was supported by R01 DK092217 [JEP-LK] from the United States’ National Institutes of Health—Diseases and Kidney (NIDDK).

DISCLOSURE
Sabine Roman serves as a paid consultant for Given Imaging/Covidien/Medtronic. John E. Pandolfini serves as a paid consultant for AstraZeneca.

AUTHOR CONTRIBUTION
SR, LK, and JEP wrote the article; JEP and LK designed the study; PK, KE, LF, and BM collected the data; SR, IH, and JEP analyzed the data; ZM performed the statistical analysis; all the authors approved the final version of the manuscript.

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