The role of pH-impedance monitoring in swallowing disorders

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Purpose of review
To review the current evidence about the usefulness and the place of pH study in the management of patients with swallowing disorders.

Recent findings
Gastroesophageal reflux disease (GERD) and laryngopharyngeal reflux (LPR) are found in approximately 30% of patients with esophageal or oropharyngeal dysphagia. Patients with suspected GERD may benefit from gastrointestinal endoscopy and proton pump inhibitors according to guidelines. The diagnosis of LPR in patients with oropharyngeal dysphagia is more controversial because there are no gold standard and diagnostic guidelines. The clinical diagnosis based on empirical therapeutic trial is a reasonable first-line strategy, but many dysphagic patients should not respond to treatment. These patients require hypopharyngeal-esophageal multichannel intraluminal impedance-pH monitoring (HEMII-pH), which is the most effective examination providing important information on GERD and LPR features. At the HEMII-pH, GERD patients often report upright (daytime) and supine (nighttime) liquid acid esophageal events with significant esophageal distal acid exposure time. LPR patients have more frequently upright (daytime) gaseous weakly acid or nonacid pharyngeal reflux events without distal esophageal acid exposure abnormalities in many times. The features of reflux at the HEMII-pH may indicate a personalized treatment for dysphagic patients combining proton pump inhibitors, alginate/magaldrate or gastroprokinetic in cases of esophageal dysmotility.

Summary
GERD and LPR are prevalent causes of dysphagia. The large number of reflux patients who do not respond to empirical treatment makes important the awareness of otolaryngologists about pH-impedance monitoring indication, features, and interpretation.

Keywords
dysphagia, gastroesophageal, head neck surgery, impedance, laryngitis, laryngopharyngeal, otolaryngology, pH study, reflux, swallowing

INTRODUCTION
Dysphagia is an increasingly frequent disorder defined as the difficulty in transferring food from the mouth to the stomach [1]. Dysphagia may be classified into esophageal and oropharyngeal dysphagia according to the location of the dysfunction. In otolaryngology, physicians are frequently faced with patients with oropharyngeal dysphagia that is related to abnormalities in the physiology of swallowing in the upper gastrointestinal tract [1,2*]. The management of swallowing disorders is an important issue because persistent dysphagia may be associated with malnutrition, dehydration, aspiration pneumonia, bronchospasm, choking, and death [3*,4]. Laryngopharyngeal reflux (LPR), gastroesophageal reflux disease (GERD) and some associated disorders are common causes of dysphagia [5]. Depending on the type of reflux (GERD versus LPR), patients may report findings of esophageal and/or oropharyngeal dysphagia. The GERD diagnosis is easily made regarding typical symptoms,
KEY POINTS

- About 30% of patients with esophageal dysphagia reported reflux disease.
- The diagnosis of gastroesophageal reflux disease (GERD) is standardized, and the usefulness of gastrointestinal endoscopy is demonstrated.
- The laryngopharyngeal reflux (LPR) clinical diagnosis based on empirical therapeutic trial is considered as a reasonable first-line strategy, but many patients with swallowing disorder and suspicion of reflux should not respond to treatment. These patients require pH study to confirm the reflux diagnosis.
- Hypopharyngeal-esophageal multichannel intraluminal impedance-pH monitoring (HEMI-pH) appears to be the most effective examination because it provides important information on GERD and LPR features.
- Most patients with GERD have upright(daytime)/supine (nighttime) liquid acid esophageal events with an esophageal distal acid exposure time >6% of testing according to Lyon consensus.
- LPR patients have more frequently upright(daytime) gaseous weakly acid or nonacid HREs, while the distal esophageal acid exposure time may be normal.
- The features of reflux at the HEMII-pH may indicate a personalized treatment for dysphagic patients.

consensus and guidelines, but the LPR diagnosis remains complicated because nonspecificity of both symptoms and signs and the lack of a gold standard examination for the diagnosis [5,6]. To date, the pH study is commonly considered as the most effective approach to demonstrate the occurrence of GERD or hypopharyngeal reflux events (HRE) and, therefore, may support the diagnosis [7,8]. In the present review, we aimed to summarize the current evidence about the usefulness and the place of pH study in the management of patients with swallowing disorders.

ETIOLOGIES OF DYSPHAGIA

The causes and the types of dysphagia (esophageal versus oropharyngeal) varied across age populations. The patient history, comorbidities and lifestyle, as well as the clinical course of dysphagia and associated-symptoms (intermittent or progressive) may help the physician to clarify the cause of the swallowing disorder. According to the medical history, the otolaryngologist may perform nasofiberoptic, transnasal esophagoscopy or fiberoptic endoscopic evaluation of swallowing (FEES) in-office for the diagnosis [15**].

In oropharyngeal dysphagia, the most common causes included laryngopharyngeal reflux; laryngeal nerve injury; some medications; neurodegenerative conditions; cricopharyngeal muscle dysfunction; Zenker’s diverticulum; cervical web; myositis; and histories of head and neck radiation or surgery [15**,16,17,18*]. The main etiologies of esophageal dysphagia are gastroesophageal reflux disease; some medications; eosinophilic or pill esophagitis; peptic stricture; cancer; achalasia and sclerodermia [15**,16,17,18*].

Reflux diseases were considered as the most prevalent conditions associated with dysphagia in many population-based or swallowing center investigations [19−22,23**]. Hoy et al. [22] evaluated 100 patients presenting in swallowing clinic and they observed that the most prevalent causes of oropharyngeal dysphagia were reflux (27%), radiation history (14%) and cricopharyngeal muscle dysfunction (11%). In 2020, Adkins et al. [23**] investigated the swallowing disorder prevalence in 31 129 individuals. Among them, 16.1% reported dysphagia with the following most prevalent causes: reflux (30.9%), eosinophilic esophagitis (8.0%) and esophageal structure (4.5%) [23**]. These study findings corroborated those of the population-based survey of Almario et al. [24] who reported in 71 812 U.S. individuals that the most common symptoms associated with dysphagia were heartburn/reflux, bloating, abdominal pain, diarrhea, and constipation. The estimation of the prevalence of LPR in patients with oropharyngeal dysphagia is however difficult because most authors did not confirm the LPR
diagnosis through the identification of hypopharyngeal reflux events (HRE) at the hypopharyngeal-esophageal multichannel intraluminal impedance-pH monitoring (HEMII-pH). About clinical presentation, dysphagia (and ‘difficulties to swallow’) was reported as one of the most prevalent symptoms in LPR patients in the largest cohort-study [25*,26,27]. Because there is no correlation between symptoms and findings, the anatomical origin of dysphagia in LPR patients remains unclear [5]. LPR patients with dysphagia may have tongue tonsil hypertrophy, edema of the retrocricoid or the laryngeal posterior commissure but the anatomical study of findings associated with dysphagia requires future large cohort studies [5,25*].

In sum, according to the recent literature findings [22,23*,24], reflux diseases appear to be prevalent conditions in the dysphagia origins.

**DIAGNOSIS OF REFLUX AND PLACE OF pH STUDY**

**Empirical therapeutic trial**

The confirmation of the reflux diagnosis in patients with dysphagia may differ from GERD to LPR patients [5]. As reported in Fig. 1, patients with esophageal dysphagia and GERD symptoms may benefit from gastrointestinal (GI) endoscopy to detect and treat esophagitis, Barrett disease or *Helicobacter pylori* infection. The GI endoscopy (and manometry) may detect another condition that may contribute to esophageal dysphagia, such as eosinophilic esophagitis, esophageal stricture or achalasia. The management of GERD is standardized and reported in recent guidelines [28–30].

The management of LPR patients remains controversial because there is no gold standard for the diagnosis. Currently, most otolaryngologists consider symptoms and nasofiberoptic findings for the baseline evaluation and they confirm the diagnosis after a positive response to a 3-month empirical therapeutic trial [31]. The ‘positive’ response consists of symptom improvement but it is subjective and the definition may substantially vary from one study to another [5,32]. For this reason, it is recommended to use validated patient-reported outcome questionnaires (e.g. reflux symptom index > 13 [33] or reflux symptom score > 13 [34]) and clinical instruments (e.g. reflux finding score > 7 [35] or reflux sign assessment > 14 [36]) to improve the clinical diagnostic accuracy and therapeutic response evaluation [37].

A recent review reported that 57% of patients exhibit improvement or relief of LPR symptoms after 3-month proton pump inhibitors (PPIs), which remains a low therapeutic success rate [38]. The reasons of nonresponse to empirical treatment include the use of inadequate treatment (i.e. PPIs in nonacid reflux), the chronic course of some LPR clinical presentations, the lack of adherence of patient to diet or medication, the inappropriate intake of medication, and the existence of differential diagnoses [38,39,40*,41]. Some differential diagnoses of reflux-like symptoms are described in Table 1.

Moreover, the nonspecificity of symptoms and findings makes uncertain the clinical diagnostic and, consequently, the use of antireflux empirical therapeutic trial may be inconsistent and costly [42*]. The HEMII-pH is indicated in nonresponder patients for two main reasons. First, the HEMII-pH is the most reliable tool to detect HRE and, therefore, confirm the diagnosis [43*]. Second, HEMII-pH may provide useful information about the presence of GERD and/or LPR; the type (acid, weakly acid, versus nonacid); the composition (gaseous, liquid, versus gaseous/liquid); and the position of patient when reflux events occur (upright versus supine) [44*,45]. To date, most otolaryngologists used twice daily PPIs for the empirical treatment [46*,47] even though most HREs are weakly or nonacid [44**,48,49]. The consideration of the reflux features is important to prescribe a more personalized treatment consisting of a combination of PPIs, alginate or magaldrate [45].

In sum, the clinical diagnosis based on empirical therapeutic trial is currently considered as a reasonable first-line strategy, but many patients with swallowing disorder and suspicion of reflux should not respond to treatment and may require objective examination to confirm the reflux diagnosis.

**Types, indications, and limits of pH study**

Many types of pH studies are commonly used worldwide in the management of patients with swallowing disorder and suspected reflux, including single, dual, triple-probe pH monitoring, hypopharyngeal/esophageal multichannel intraluminal impedance-pH monitoring, Bravo pH monitoring, and oropharyngeal pH monitoring. According to the characteristics of the devices (number and positions of pH/impedance sensors, etc.), the information provided by the pH study may vary. From a practical standpoint, the pH study is usually performed over a 24-h period. Patients may report inconvenience, but the tolerance is usually adequate [50]. The difficulties related to the placement of the pharyngeal sensor(s) and the probe movements during swallowing are both considered as the main weaknesses of the pH study [50,51]. Moreover, it was long time suggested that drying of the pharyngeal sensors may lead to pseudoreflux and false positive results but this finding was poorly demonstrated [51].
Single, dual- or triple-probe esophageal pH monitoring

Single esophageal probe pH monitoring is commonly used in gastroenterology for the GERD diagnosis that is based on distal esophageal acid exposure. Dual-probe pH monitoring (with the proximal sensor placed in upper esophagus or pharynx) was developed for LPR and was used in the first study differentiating LPR from GERD [52]. When the reflux is suspected as the main cause of the patient...
dysphagia, practitioners have to keep in mind that LPR may occur without abnormal distal esophageal acid exposure. Indeed, Murris et al. [51] reported that 24% of patients with LPR findings (>1 HRE) had normal acid exposure in the low esophagus. They also reported that 68% of distal-to-proximal esophageal reflux events reached pharynx [51]. The lack of association between distal esophageal and pharyngeal acid events was supported by the study of Postma et al. [53] who found that 38% of LPR patients (>1 HRE) had normal esophageal acid exposure times. The pH-impedance monitoring differences between GERD and LPR are summarized in Table 2. The accuracy of single, dual- or triple-probe pH studies without impedance ring is called into question regarding the inability of devices to detect weakly acid or nonacid reflux events [5].

### Multichannel intraluminal impedance-pH monitoring

Multichannel intraluminal impedance-pH monitoring (MII-pH) is available with or without pharyngeal impedance sensors. MII-pH is indicated in GERD patients with a suspicion of nonacid distal reflux, in which bile acids may be involved in the development of esophageal lesions [54,55]. Interestingly,
two studies using pH-impedance monitoring reported the back flow of gastroduodenal content into the pharynx, and measurable bile acids in the saliva [56,57]. The detection of bile acids in the saliva supports the potential occurrence of duodenogastric reflux events in LPR patients even if this though was never studied. According to the high prevalence of LPR in GERD patients, and the involvement of both GERD and LPR in the development of swallowing disorders, the use of HEMII-pH makes sense rather than the MII-pH without pharyngeal sensors [5]. Indeed, the HEMII-pH provides useful information about GERD and LPR [5].

To date, there are no international guidelines establishing normative data for HRE at the HEMII-pH (diagnostic criteria). A few studies investigated the HEMII-pH findings in healthy individuals (Table 3) [58,59,60–73]. Kim et al. [74] observed that the consideration of ≥1 HRE was associated with sensitivity and specificity of 76.0% and 81.5%, respectively, whereas others reported a normal range of 1–10 HREs [58,68]. The diagnosis criteria may vary regarding the type of pH study device used. The findings of a recent systematic review suggested that the 95th percentile thresholds were 10–73 events for proximal esophageal reflux event, 0–10 for HREs, and 40–128 for events with pH < 6.0 on oropharyngeal pH monitoring [58**]. The diagnosis criteria may vary regarding the type of pH study device used. The findings of a recent systematic review suggested that the 95th percentile thresholds were 10–73 events for proximal esophageal reflux event, 0–10 for HREs, and 40–128 for events with pH < 6.0 on oropharyngeal pH monitoring [58**].

Profiles of reflux patients at the hypopharyngeal-esophageal multichannel intraluminal impedance-pH monitoring

The profile of LPR patients at the HEMII-pH was recently investigated in few studies [43*,44**,48,49,75]. In 2021, we observed that 74% of HREs occurred outside 1-h postmeal times, whereas 20.5% and 5.5% events occurred during the 1-h postmeal and nighttime, respectively (Fig. 2) [44**]. In another study, authors found that more than 44.5% of patients reported weakly acid or nonacid LPR [75], which were defined according to the ratio of number of acid HREs (pH < 4.0)/number of nonacid (pH > 4.0) HREs through the 24-h testing period. Patients with a ratio of acid/nonacid HREs < 0.5 were considered as individuals with nonacid LPR, while those with a ratio between 0.5 and 2.0 had weakly acid LPR [75]. HREs occurred upright and daytime in 59% of cases [44**,75]. In practice, the pH of the reflux event may increase from the distal to the proximal esophagus and pharynx. Sikavi et al. [76] observed that the occurrence of

<table>
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<tr>
<th>Impedance-pH monitoring features</th>
<th>GERD</th>
<th>LPR</th>
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<tr>
<td>Distal esophageal reflux</td>
<td>Mostly acid</td>
<td>Normal in 30–50%</td>
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<td>Frequent events</td>
<td></td>
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<tr>
<td>Mostly liquid</td>
<td></td>
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<tr>
<td>Upright and supine</td>
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<td>Increased in supine position</td>
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<tr>
<td>Mostly postmeal time</td>
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<td>Lyon &amp; DeMeester criteria</td>
<td></td>
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<tr>
<td>Proximal esophageal/pharyngeal events</td>
<td>Infrequent</td>
<td>&gt;1 events (HEMII-pH)</td>
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<tr>
<td>If present: mostly acid</td>
<td>Weakly/nonacid events</td>
<td></td>
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<tr>
<td>Mostly gaseous events</td>
<td>Upright and daytime</td>
<td></td>
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<tr>
<td>Outside the postmeal time</td>
<td></td>
<td></td>
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<tr>
<td>Contributing factors</td>
<td>Supine position</td>
<td>Hiatal hernia (resistance to treatment)</td>
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<td>Hiatal hernia</td>
<td>LES and UES insufficiencies</td>
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<td>LES insufficiency</td>
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<tr>
<td>Correlation between symptoms-events</td>
<td>Frequently significant</td>
<td>Rarely significant</td>
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GERD, gastroesophageal reflux disease; HEMII-pH, hypopharyngeal-esophageal multichannel intraluminal impedance-pH monitoring; L/UES, lower/upper esophageal sphincter; LPR, laryngopharyngeal reflux.
daytime, upright and gaseous HREs was commonly associated with transient relaxations of the lower and upper esophageal sphincters. In another recent study, these authors reported that 43.3% of patients with >1 HREs reported abnormal findings at the high-resolution manometry; the most common abnormality being the ineffective esophageal motility, whereas most patients having reduced proximal esophageal contractibility [77]. The findings of these recent studies support the observations of studies conducted over the past decade [61,74]. Regarding GERD, the patient profile at the HEMII-pH is mostly characterized by upright (daytime)/supine (night-time) liquid acid esophageal events, with an esophageal distal acid exposure time >6% of testing according to Lyon consensus [29].

According to the upright and weakly/nonacid profile of LPR patients, the use of twice daily PPIs for the empirical therapeutic trial in dysphagic patients with a suspicion of LPR may be put into question. Indeed, the second PPI intake (before dinner) was proposed to reduce the acid stomach production during the evening and the night [77]. Moreover, PPIs do not change the number and duration of reflux events. PPIs only increase the pH of reflux events (that are already weakly acid in pharynx), whereas alginate or magaldrate reduce the number of reflux events; acting on acid, weakly acid and nonacid esophageal and hypopharyngeal reflux events [78]. Thus, practitioners may consider more frequently the combination of PPIs with alginate or magaldrate, or alginate/magaldrate only in the

| Table 3. Normative values (median/mean/number of positive individuals) for pH-impedance study or oropharyngeal pH monitoring |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| References      | Device          | Sample features | PRE/HRE event features | Results        |
| Shay, 2004 [70] | 24-h MII-pH     | N = 60 HIs      | Total/upright/supine PRE (median) | 8/7/0          |
| Zentilin, 2006 [71] | 24-h MII-pH     | N = 25 Hls      | Proximal events (median) | 15             |
| Xiao, 2009 [60] | 24-h MII-pH     | N = 70 Hls      | Total/upright/supine PRE (median) | 8/8/0          |
| Wang, 2011 [59] | 24-h HEMII-pH   | N = 37 Hls      | Acid/weakly acid/nonacid (median) | 1/0/1          |
| Hoppo, 2012 [61] | 24-h HEMII-pH   | N = 40 Hls      | Total/upright/supine HRE (median) | 0/0/0          |
| Desjardin, 2013 [62] | 24-h HEMII-pH   | N = 45 Hls      | PRE events pH <4; pH <5 (number) | 1/1            |
| JettO, 2014 [72] | 24-h MII-pH     | N = 142 Hls     | Acid/weakly acid/nonacid (mean) | 24/15/9        |
| Kawamura, 2016 [73] | 24-h MII-pH     | N = 42 Hls      | Total/upright/supine PRE (median) | 16/35/1        |
| Hou, 2020 [64]  | 24-h HEMII-pH   | N = 38 Hls      | Total/acid/nonacid HRE (median) | 0/0/0          |
| Do, 2020 [65]   | 24-h HEMII-pH   | N = 21 Hls      | PRE/HRE information | NP             |
| Sun, 2009 [66]  | Oropharyngeal pH metry | N = 20 Hls | HRE-pH <4; pH <5 (median) | 0/0            |
| Ayazi, 2009 [68] | Oropharyngeal pH metry | N = 55 Hls | HRE-pH <4; <5; <5.5 (median) | 0/0/0          |
| Chheda, 2009 [69] | Oropharyngeal pH metry | N = 20 Hls | HRE-pH <4; <4.5; <5; <5.5 (median) | 0/0/0/1        |
| Feng, 2014 [63] | Oropharyngeal pH metry | N = 29 Hls | HRE (median/mean/number) | NP             |
| Yadlapati, 2016 [67] | Oropharyngeal pH metry | N = 18 Hls | Abnormal % time pH <5/5.5 (mean) | 0/3            |

HEMI-pH, (hypopharyngeal-esophageal) multichannel intraluminal impedance-pH monitoring; HIs, healthy individuals; HRE, hypopharyngeal reflux events; N, number; NP, not provided; PRE, proximal esophageal reflux events.
empirical therapeutic trial. Alginate and magaldrate may be also used in the post-HEMII-pH personalized treatment of patients with swallowing disorder [42,45]. Patients with esophageal dysmotility and reflux may also benefit from gastroprokinetic, but the identification of motility disorders requires high-resolution manometry examination.

**Oropharyngeal pH monitoring**

Oropharyngeal pH monitoring (Restech Dx-pH monitoring) was developed for the diagnosis of LPR [68]. To date, a positive Ryan score (upright score ≥ 9.41 or supine score ≥ 6.8) is considered as relevant for the LPR diagnosis. Ryan score is calculated considering the following components: the percentage time pH < 5.5 upright or < 5.0 supine, the number of episodes in which the pH dropped below threshold and the duration of the longest episode [66,68,69]. The accuracy of Ryan score was however controversial because the score does not consider events with pH > 7, which are frequent in LPR patients. Vance et al. [79] compared both diagnostic approaches in 77 patients who benefited from HEMII-pH and oropharyngeal pH monitoring throughout the same 24-h period. The comparison between HEMII-pH and oropharyngeal pH monitoring revealed that oropharyngeal pH monitoring detected more percentage time/total pharyngeal reflux events in supine and upright positions and longer event times than HEMII-pH; whereas HEMII-pH testing was able to detect more events of pH < 4 than oropharyngeal pH monitoring [79]. Moreover, oropharyngeal pH monitoring correlated better with total patient symptom scores including cough, heartburn, burping, and throat clearing, than HEMII-pH [79]. In practice, the main weakness of oropharyngeal pH monitoring is the lack of information about esophageal findings and GERD. The
limitation is important because patients with severe GERD have a higher probability to have severe LPR and both esophageal and oropharyngeal dysphagia [75].

Placement and technical point
The distal sensor of HEMII-pH is usually placed 5 cm above the lower esophageal sphincter and the pharyngeal sensor is placed 1-2 cm above the upper esophageal sphincter [58**]. The placement of the probe (and the hypopharyngeal sensors) may be controlled with chest radiography, nasofibroscopy, or through a high-resolution manometry. The placement of the pH-study probe may be difficult in patients with swallowing disorder because it requires the need of swallow the probe. The analysis of HEMII-pH tracing may be automated but Kang et al. [80] found that the automated analysis was associated with a tendency of excessive reflux measurement when compared with manual analysis by experienced practitioners.

CONCLUSION
Gastroesophageal reflux disease and laryngopharyngeal reflux are both prevalent causes of esophageal and oropharyngeal dysphagia. The large number of reflux patients who do not respond to empirical treatment makes important the awareness of otolaryngologists about pH-impedance monitoring. HEMII-pH is probably the most relevant pH study for patients with swallowing disorder because it provides useful information about esophageal (GERD) and pharyngeal (LPR) reflux events and may indicate a personalized treatment using PPIs, alginate or magaldrate.

Acknowledgements
None.

Financial support and sponsorship
None.

Conflicts of interest
There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING
Papers of particular interest, published within the annual period of review, have been highlighted as:
- of special interest
- of outstanding interest

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This study compared pH-impedance monitoring with oropharyngeal pH monitoring.