

# Doença do refluxo faringolaríngeo: Serão os sintomas preditivos dos achados endoscópicos?

## Pharyngolaryngeal reflux disease - Can symptoms predict endoscopic findings?

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### RESUMO

**Objectivos:** correlacionar a severidade da sintomatologia com os achados endoscópicos faringo-laríngeos em indivíduos com doença do refluxo faringo-laríngeo (DRFL).

**Desenho do Estudo:** estudo unicêntrico, observacional e prospectivo.

**Material e Métodos:** 109 adultos recorreram à consulta de ORL ou de Gastroenterologia do Hospital de Braga entre Abril e Outubro de 2019 com sintomas suspeitos de DRFL. Através da aplicação de dois questionários para diagnóstico de DRFL - o Reflux Symptom Index (RSI) e o Reflux Finding Score (RFS) – obteve-se uma amostra final de 39 indivíduos. Todos os indivíduos foram ainda submetidos a endoscopia digestiva alta e impedancio-pH-metria esofágica.

**Resultados:** O sintoma mais frequente foi o pigarro (3,64). O score médio do RSI foi de 23,4±9.1. A presença de eritema/hiperemia ( $p=.036$ ) e a obliteração ventricular ( $p=.015$ ) correlacionaram-se com a presença de sintomas como disfonia. O diagnóstico de DRGE foi confirmado em 33% dos casos. A tosse após deitar foi o único sintoma que se associou a maior incidência de RGE ( $p=.01$ ).

**Conclusões:** Os autores concluíram que existe correlação entre os achados endoscópicos e os sintomas de RFL.

**Palavras-chave:** Refluxo faringolaríngeo; Refluxo gastro-esofágico; Laringoscopia; Avaliação de sintomas

### ABSTRACT

**Aim:** to correlate the severity of symptoms with pharyngolaryngeal endoscopic findings in individuals diagnosed with pharyngolaryngeal reflux disease (PLRD).

**Design of the study:** unicentric, observational and prospective study.

**Material and Methods:** 109 adults attended the ENT and Gastroenterology consultation at Hospital de Braga between April and October 2019 with suspected symptoms of PLRD. Through the application of two questionnaires - the Reflux Symptom Index (RSI) and the Reflux Finding Score (RFS) – a final sample of 39 patients was obtained. All individuals were also submitted to upper digestive endoscopy and esophageal pH impedance.

**Results:** The most frequent symptom was throat clearing (3,64). The average RSI score was 23.4±9.1. The laryngoscopic findings that most correlated with the presence of symptoms (namely dysphonia) were erythema/hyperemia ( $p=.036$ ) and the presence of ventricular obliteration ( $p=.015$ ). The diagnosis of GERD was confirmed in 13 patients (33%). Cough after lying down was the only symptom that was associated with a higher incidence of GERD ( $p=.01$ ).

**Conclusions:** The authors concluded that there is a correlation between some findings at laryngoscopy and symptoms of PLR.

**Keywords:** Laryngopharyngeal Reflux; Gastro-Esophageal Reflux; Laryngoscopy; Symptom Assessment

### INTRODUCTION

The term “pharyngolaryngeal reflux” (PLR) is often used by otorhinolaryngologists in order to describe laryngeal findings and symptoms of irritation in patients with chronic pharyngo-laryngeal symptoms. This extra-esophageal manifestation of gastroesophageal reflux disease (GERD) was first named by Koufman and Cummins (1994) to highlight the importance of symptoms and changes in the laryngopharyngeal segment in patients with gastro-esophageal reflux<sup>1</sup>. The concept of “pharyngolaryngeal reflux disease” (PLRD), introduced in 2002 by the American Academy of Otolaryngology and Head and Neck Surgery, is currently a new established and autonomous clinical entity that most otorhinolaryngologists use to describe these symptomatic and mucosal alterations<sup>2</sup>. Despite acid reflux can contribute to posterior laryngitis in up to 80% of cases, there are other situations that can mimic typical PLR symptoms such as infections, vocal

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Artigo recebido a 11 de Outubro 2020. Aceite para publicação a 24 de Novembro de 2020.

abuse, allergy, smoking, inhaled environmental irritants, and alcohol abuse<sup>3</sup>. As such, typical symptoms of PLR like chronic cough, dysphonia, dysphagia, odynophagia, hoarseness or pharyngeal globus are very unspecific, although very common in our clinical practice. Some situations frequently encountered in clinical practice, such as chronic sinusitis, laryngitis and pharyngitis, chronic oedema of the vocal folds, glottic contact ulcer, laryngeal granulomas, tooth caries, precancerous lesions and pharyngo-laryngeal neoplasms also seem to be related in some degree to PLR<sup>4-6</sup>. Although, definitive data about the incidence of PLR is lacking, and the diagnostic and therapeutic regimen has not been standardized so far. Gastroesophageal reflux disease is a common disease, with an empirical diagnosis and an estimated prevalence of 8% to 33%. GERD diagnosis can manifest through tissue damage (esophagitis, strictures...) or troublesome symptoms like heartburn, acid reflux and regurgitation, which are the major symptoms. A favorable response to proton pump inhibitor (PPI) therapy supports its diagnosis<sup>7</sup>. As we have said before, GERD can also produce symptoms and signs of tissue injury within the oropharynx, larynx and respiratory tract being responsible for atypical or extra-esophageal symptoms. Currently, current standard diagnostic tool of GERD is 24h-esophageal pH-impedance monitoring, which can detect both acid and non-acid reflux events<sup>8</sup>. Currently there is no gold standard for a definitive diagnosis of PLR. Double probe ambulatory pH monitoring was accepted as the gold standard technique for PLR diagnosis for many years. However, a negative result should not exclude the presence of PLR and the degree of symptoms and signs may not correlate with pH monitoring results<sup>9</sup>. Systematic endoscopic visualization of the pharynx and larynx can improve diagnostic accuracy. Again, although most findings are nonspecific, thickness, redness, and swelling located in the posterior regions of the larynx and hypopharynx suggest that reflux is the etiology of the inflammation. Because of that, Belafsky et al (2001) developed an objective scale, Reflux Finding Score (RFS), based on findings on pharyngolaryngoscopic exam. It consists of a score determined by the examiner based on eight findings: subglottic edema, ventricular obliteration, erythema/hyperemia, vocal fold edema, diffuse laryngeal edema, posterior commissure hypertrophy, granuloma/granulation tissue, and thick endolaryngeal mucus. The score, which ranges from 0 to 26, indicates PLR if greater than 7<sup>10</sup>.

Due to low specificity of PLR symptoms, a symptom scale (Reflux Symptom Index [RSI]) was also developed by Belafsky et al (2002) to improve diagnostic skills and help us in follow-up. This is a self-administered questionnaire that evaluates the severity of several complaints such as hoarseness, throat mucus, swallowing difficulties, cough, breathing difficulties, pharyngeal globus or heartburn. As cited by several authors, scores superior or equal to 13 are clinically significant and may be indicative of PLR<sup>11</sup>.

For all this uncertainties, this prospective study aims to correlate pharyngolaryngeal endoscopic findings (using the RFS) with symptoms of reflux pharyngolaryngitis (using the RSI) and to determine the performance of the current tools (RSI and RFS) used to diagnose PLR. Secondly, the authors intend to estimate the prevalence of GERD diagnosis in patients with confirmed PLR. Answering these questions we can better understand which are the signs that best correlate to the main symptoms of PLR.

## MATERIAL AND METHODS

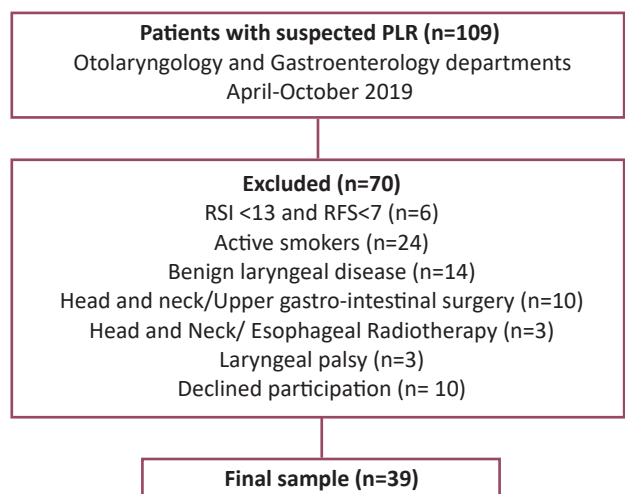
### Type of study

A unicentric, observational and prospective analysis was performed between April and October 2019 in the Otorhinolaryngology and Head and Neck Surgery and Gastroenterology departments of Hospital de Braga.

### Patient selection

Initially and during that period, the authors included all patients (n=109) over the age of 18 who were evaluated in general Otorhinolaryngology and Dysphagia hospital consultations due to symptoms suggestive of pharyngolaryngeal reflux disease (cited above). Patients meeting any of the following criteria were excluded: RSI score inferior to 13 and RFS score inferior to 7, active smokers, presence of benign laryngeal conditions, history of head and neck and upper gastrointestinal surgery or radiotherapy, confirmation of laryngeal palsy and incapacity to understand or accept the study protocol. In total, 39 patients with confirmed pharyngolaryngeal reflux were included according to clinical symptoms and signs. Study flow diagram is showed in figure 1.

**FIGURE 1**  
Study flow diagram



PLR = Pharyngolaryngeal reflux  
RSI = Reflux Symptom Index  
RFS = Reflux Finding Score

### Assessment of symptoms

Reflux Symptom Index questionnaire was applied in all patients (table 1). For that, the investigators used the translated version to Portuguese (validated by Eckley *et al*) and helped the patients filling the questionnaire in order to minimize the risk of misinterpretation<sup>12</sup>. The RSI questionnaire is a widely used and approved, self-administered, 9-item questionnaire for the assessment of symptoms in PLR patients. It consists of questions about the presence and intensity of hoarseness, throat clearing, postnasal drip, difficulty with swallowing, coughing, breathing difficulty, troublesome cough, lump sensation, and heartburn. Each symptom was scored from 0 (no problem) to 5 (very troublesome problem). According to normative available data, the authors considered a RSI  $\geq 13$  as clinically significant and indicative of PLR<sup>10</sup>.

The authors also searched for GERD symptoms, such as heartburn, difficulty swallowing, regurgitation of food or sour liquid and chronic cough.

**TABLE 1**

Reflux Symptom Index

During the last month, how did the following problems affect you? 0 = No problem 5 = Severe problem/very troublesome	
Hoarseness or a problem with your voice	1 2 3 4 5
Clearing your throat	1 2 3 4 5
Excess throat mucus or postnasal drip	1 2 3 4 5
Difficulty swallowing food, liquids, or pills	1 2 3 4 5
Coughing after you ate or after lying down	1 2 3 4 5
Breathing difficulties or choking episodes	1 2 3 4 5
Troublesome or annoying cough	1 2 3 4 5
Sensations of something sticking in your throat or a lump in your throat	1 2 3 4 5
Heartburn, chest pain, indigestion, or stomach acid coming up	1 2 3 4 5

### Endoscopic evaluation

Reflux Finding Score was assessed through pharyngolaryngeal endoscopy (with a flexible laryngoscope Xion®, EF-N, 0482). Item scores range from 0 to 4 and are determined by eight laryngoscopic main findings: erythema or hyperemia, diffuse laryngeal and subglottic edema, ventricular obliteration, vocal fold edema, posterior commissure hypertrophy, granuloma/granulation tissue, and the presence of thick endolaryngeal mucus (table 2). The total score ranges from 0 to 26. In this case, the authors considered an RFS  $\geq 7$  as a high probability score for PLR diagnosis<sup>11</sup>.

To minimize inter-observer variability, all endoscopies were performed by the same examiner.

**TABLE 2**

Reflux Finding Score

<b>Subglottic edema</b>	Absent(0) Present (2)
<b>Ventricular obliteration</b>	Partial (2) Complete (4)
<b>Erythema/hyperemia</b>	Arytenoids only (2) Diffuse (4)
<b>Vocal fold edema</b>	Mild (1) Moderate (2) Severe (3) Polypoid (4)
<b>Diffuse laryngeal edema</b>	Mild (1) Moderate (2) Severe (3) Obstructing (4)
<b>Posterior commissure hypertrophy</b>	Mild (1) Moderate (2) Severe (3) Obstructing (4)
<b>Granuloma/granulation tissue</b>	Absent (0) Present (2)
<b>Thick endolaryngeal mucus</b>	Absent (0) Present (2)

### Gastrointestinal evaluation

Our selected final sample of 39 patients was also submitted to upper gastrointestinal endoscopies (UGE), under sedation, after completing the questionnaires. Esophageal pH-impedance 24 hours monitoring (imp-pH) was also performed in order to confirm or preclude the presence of GERD. Based on Lyon Consensus, the authors considered an acid exposure time (AET)  $<4\%$  as normal. Borderline GERD was considered when AET was between 4 and 6% or  $\geq 40$  reflux episodes per 24 hours. Confirmation of GERD was done through visualization of esophageal macroscopic alterations on UGE and when AET was  $\geq 6\%$  or  $\geq 80$  reflux episodes on imp-pH13, according to the Rome IV criteria.

All patients were asked to stop the PPI therapy for approximately 14-21 days before the procedures. Sample was divided in three major groups: RSI  $\geq 13$  vs  $<13$ , RFS  $\geq 7$  vs  $<7$  and GERD vs non-GERD.

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethic Commission for the Investigation on Life and Health Sciences, University of Minho and Ethics Committee for Health of Braga Hospital. Written informed consent was obtained from all patients. The software used was SPSS® 26.0 (Statistical Package for the Social Science). The Pearson correlation coefficient for parametric variables was used to assess the degree of correlation, and to reject the null hypothesis,  $p \leq 0.05$  was used.

## RESULTS

Over the study period, 39 participants were included. The average age of patients was 57.7 years, ranging between 31 and 83 years. Other sociodemographic and clinical

data of the patients is listed in table 3. The majority of patients were women (87,2%).

As shown in table 4, the most frequent and intense symptoms were throat clearing (absent in only 2,9%) followed by hoarseness or a problem with the voice (absent in 4 patients) and the less common was difficulty swallowing solids, liquids or pills (absent in 59% of patients). All patients showed RSI scores superior or equal to 7 and the average score was 23,4 (SD 9,1), ranging from 7 to 42 points).

The endoscopic results revealed that all patients had pharyngo-laryngeal erythema/hyperemia and 64,1% (n=25) presented posterior commissure hypertrophy. Subglottic edema was found in only one case. The average score of RFS was 11 (SD 2,9) (ranging from 7 to 17 points). Reflux Finding score results are listed in table 5.

**TABLE 3**

Sociodemographic and clinical data

Age, mean (SD), years	57,7 (11,7)
<b>Gender</b>	
Male, n (%)	5 (12,8)
Female, n (%)	34 (87,2)
<b>Symptoms</b>	
Extraesophageal only, n (%)	3 (7,7)
Esophageal and extraesophageal, n (%)	36 (92,3)
<b>History of anxiety/depression, n (%)</b>	17 (43,6%)

**TABLE 5**

Reflux Finding Score results

	Male	Female	Total
<b>Subglottic Edema</b>			
Absent, n (%)	5	33	38 (97,4)
Present, n (%)	0	1	1 (2,6)
<b>Ventricular Obliteration</b>			
Complete, n (%)	0	0	0
Partial, n (%)	1	37	38 (97,4)
Absent, n (%)	0	1	1 (2,6)
<b>Erythema/Hyperemia</b>			
Arytenoids only, n (%)	2	16	18 (46,2)
Diffuse, n (%)	3	18	21 (53,8)
<b>Vocal Fold Edema</b>			
Absent, n (%)	2	14	25 (64,1)
Present, n (%)	3	11	14 (35,9)
<b>Diffuse Laryngeal Edema</b>			
Absent, n (%)	3	22	25 (64,1)
Present, n (%)	2	12	14 (35,9)
<b>Posterior Commissure Hypertrophy</b>			
Absent, n (%)	2	12	14 (35,9)
Present, n (%)	3	22	25 (64,1)
<b>Granuloma/Granulation tissue</b>			
Absent, n (%)	3	28	31 (79,5)
Present, n (%)	2	6	8 (20,5)
<b>Thick Endolaryngeal Mucus</b>			
Absent, n (%)	2	18	20 (51,3)
Present, n (%)	3	16	19 (48,7)
<b>Total RFS score, mean (SD)</b>	<b>11 (2,9)</b>		
<b>RFS maximum score</b>	<b>17</b>		
<b>RFS minimum score</b>	<b>7</b>		

**TABLE 6**

Correlation between symptoms and endoscopic pharyngo-laryngeal findings (p-values)

	Subglottic edema	Ventricular obliteration	Erythema/hyperemia	Posterior commissure hypertrophy	Thick endolaryngeal mucus	Granuloma or granulation tissue	Diffuse laryngeal edema	Vocal fold edema
Hoarseness or a problem with your voice	0,760	<b>0.015*</b>	<b>0.036*</b>	0.088	0.711	0.077	0.244	0.360
Clearing your throat	0.797	0.052	0.726	0.937	0.789	0.243	0.444	0.240
Excess throat mucus or postnasal drip	0.479	0.479	0.290	0.904	0.658	0.594	0.982	0.811
Difficulty swallowing food, liquids, or pills	0.428	0.436	0.227	0.765	0.432	0.553	0.257	0.250
Coughing after you ate or after lying down	0,253	0.316	0.466	0.498	0.924	0.205	0.156	0.632
Breathing difficulties or choking episodes	0.988	0.256	<b>0.032*</b>	0.512	0.716	0.788	0.459	0.632
Troublesome or annoying cough	0.578	0.354	0.140	0.865	0.177	0.436	0.780	0.575
Sensations of something sticking in your throat or a lump in your throat	0.330	0.947	0.782	0.279	0.372	0.150	0.223	0.078
Heartburn, chest pain, indigestion, or stomach acid coming up	0.701	0.196	0.935	0.774	0.746	0.156	0.950	0.623

\*p&lt;0.05

**TABLE 7**

Presence of GERD

GERD (borderline+proven)	
Absent, n (%)	18 (46,2)
<b>Present, n (%)</b>	<b>13 (33,3)</b>
Missing, n (%)	8 (20,5)
GERD (proven)	
Absent, n (%)	20 (51,3)
<b>Present, n (%)</b>	<b>5 (12,8)</b>
Missing, n (%)	14 (35,9)

Lyon Consensus based on 24 hours pH-metry:

Normal: acid exposure time &lt;4%.

Borderline: AET 4-6% or ≥ 40 reflux episodes.

Proven: AET ≥ 6% or ≥ 80 reflux episodes.

In total, 28% presented RSI ≥ 13 and RFS ≥ 7 and 100% presented RSI ≥ 13 or RFS ≥ 7.

Correlations between symptoms and endoscopic pharyngolaryngeal findings are listed in table 6. The authors concluded that eritema/hyperemia correlated positively and significantly with hoarseness (p=.036) and breathing difficulties (p=.032). Hoarseness was also correlated with the presence of ventricular obliteration (p=.015).

Within the 39 patients we established two groups: GERD and non-GERD. We end up with 13 GERD (33%), 18 Non-GERD (46%) and 8 unclassified patients

(haven't performed pH impedance). We didn't found statistically significant differences between age (p=.25) or sex (p=1.00) on GERD diagnosis. The classification of symptoms as extraesophageal only or extraesophageal plus esophageal wasn't helpful in distinguishing both groups. The RSI score differences wasn't significant between GERD and non-GERD groups (p=0.1) but we found significant differences between coughing after lying down (p=.01), greater in the GERD group. The RFS differences were also insignificant (p=.76).

## DISCUSSION

Failing to recognize PLR in patients with chronic symptoms can contribute to complications such as contact ulcers, granulomas, symptomatic subglottic stenosis, lower airway disease, laryngeal cancer and are more susceptible to damage from intubation. On the other hand, because typical PLR symptoms are nonspecific and can also be caused by infections, vocal abuse, allergy, smoking, inhaled environmental irritants, and alcohol abuse, heightened awareness of PLR can lead to overdiagnosis, leading to unnecessary costs and missed diagnoses<sup>1,4,9,14</sup>. Despite the evidence that favors the association, there is no method that demonstrates a clear causal relationship between reflux and laryngitis. Despite scientific evidence showed that PLR is not an advanced stage of GERD, we know that the laryngeal mucosa is more acid-sensitive than the esophagus. In addition to this, one third of PLR



patients have GERD<sup>9</sup>. Some questions remain unclear, and, so far it is not known if it is GERD that cause PLR or if they are concomitant diseases with similar or independent underlying mechanisms.

Many studies advocate that the application of the RSI in groups of patients with a suspicion of PLR is easy, fast and highly reproducible and that RSI score is higher in patients with PLR or PLR and GERD when compared with GERD alone and with controls<sup>10,15</sup>. In the present study, symptoms and RSI scores didn't show clinical correlation with the presence of GERD, but we found a positive correlation with coughing after lying down, which was undoubtedly the main symptom of clinical alertness. On the other hand, in the present study there were patients with only extraesophageal symptoms that were subsequently diagnosed with GERD, which means GERD cannot be excluded based only on the absence of esophageal symptoms.

Laryngoscopic nonspecific signs of laryngeal irritation and inflammation are usually seen in these patients, but findings can be ambiguous and asymptomatic individuals can reveal findings similar to those with proven PLR. However, RFS has demonstrated high reproducibility and reliability in other studies and a patient which scores  $\geq 7$  points has 94% probability of presenting PLR. Moreover, it was shown that RFS and RSI are mutually complementary to each other and only a small percentage of patients who score positive in RSI score negative in RFS and vice versa<sup>16</sup>. However, in our sample, only 28% presented RSI  $\geq 13$  and RFS  $\geq 7$ . The symptoms most frequently found were the presence of hoarseness, throat clearing and heartburn/regurgitation. Only one of these (hoarseness) had a strong positive correlation to laryngoscopic findings (eritema/hyperemia). However, the presence of breathing difficulties showed a positive correlation to eritema/hyperemia.

Vázquez de la Iglesia et al studied a population with symptoms highly suggestive of PLRD (RSI scores greater than 13 and also suspicious laryngoscopic findings (RFS scores greater than 7) and concluded that the laryngoscopic findings are most useful for diagnosis and patients' symptoms are most useful for follow-up and evolution of medical treatment<sup>15</sup>. They also recommended empirical treatment with PPI in full dose (daily administration of the highest dose before breakfast, i.e. 40 mg for omeprazol, pantoprazol, and lansoprazol, and 30 mg for esomeprazol) for 4 months. Dysphonia that is more common in the morning has been reported by some authors as a major symptom of PLRD. According to their theory, that happens because of vocal cord edema caused by night reflux episodes, improving during the day<sup>17</sup>. In fact, in our study, hoarseness was the most frequent and intense symptom (average score of 3,54) and correlated with ventricular obliteration and laryngeal eritema/hyperemia. However, we found a weak positive correlation between hoarseness and vocal fold edema.

New effective, sensitive and specific methods to diagnose PLR patients are being developed. The Dx-pH measurement system is a new minimally invasive way to monitor for acid reflux in the airway, posterior larynx and esophagus during sleep<sup>18,19</sup>. The detection of salivary pepsin has also been proposed as a biomarker for the diagnosis of PLR (in normal situations, it does not exist in the airway). Pepsinogen is secreted by the stomach's chief cells and converted into pepsin in acid conditions. Nevertheless, current evidence for salivary pepsin use is still insufficient<sup>20</sup>.

## CONCLUSION

Both Reflux Finding Score and Reflux Symptom Index questionnaires have demonstrated to be highly reproducible and reliable, with high specificity for PLR diagnosis. The authors concluded that pharyngo-laryngeal eritema and hyperemia correlated positively and significantly with symptoms of hoarseness and breathing difficulties. Hoarseness was also correlated with the presence of ventricular obliteration. We also concluded that one third of the patients with PLRD also had confirmed GERD. Also, we found that cough after lying down is undoubtedly the main symptom of clinical alertness of GERD in patients with extraesophageal symptoms.

## Conflict of interests

The authors declare that they have no conflict of interests to declare.

## Data confidentiality

The authors declare that they followed the protocols of their work in publishing patient data.

## Protection of people and animals

The authors declare that the procedures followed are in accordance with the regulations established by the directors of the Commission for Clinical and Ethical Research and in accordance with the Helsinki Declaration of the World Medical Association.

## Privacy policy, informed consent and Ethics Committee Authorization

The authors declare that they have written consent for the use of photographs of patients in this article.

## Financing

This work did not receive any contribution, funding or scholarship.

## Availability of scientific data

There are no publicly available data sets related to this work.

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