Chronic Cough and Pulmonary Manifestations of Laryngopharyngeal Reflux Disease

Aaron J. Jaworek, MD[a], Thomas L. Carroll, MD[b,*]

KEYWORDS

• Chronic cough • Refractory chronic cough • Laryngopharyngeal reflux • Pulmonary • Respiratory • Gastroesophageal reflux disease

KEY POINTS

- Chronic cough can have a detrimental impact on physical and mental health as well as unwanted socioeconomic consequences.
- Reflux treatment is important to optimize in management of certain refractory respiratory diseases including chronic cough, asthma, chronic obstructive pulmonary disease, interstitial lung disease, and lung transplantation.
- For definitive evaluation of reflux, testing with hypopharyngeal-esophageal multichannel intraluminal impedance with dual-PH sensor and high-resolution esophageal manometry is an important step when empiric treatment trials for reflux have failed and the etiology remains elusive.

INTRODUCTION

Chronic cough (CC), defined as cough lasting more than 8 weeks, is estimated to affect approximately 10% of the world's population, with higher rates in Europe, North America, and South America.[1] Of 74,977 respondents to the 2018 National Health and Wellness Survey (NHWS), 4.9% reported experiencing chronic cough in the previous 12 months. The weighted 12-month prevalence rate was 5.0% which is equivalent to approximately 12.3 million US adults. Prevalence was slightly higher in females (5.2%) than males (4.7%) and increased with age and history of smoking.[2]

[a] St. Luke's University Health Network and Specialty Physician Associates, Bethlehem, PA, USA; [b] Division of Otolaryngology–Head and Neck Surgery, Brigham and Women's Hospital, Department of Otolaryngology–Head and Neck Surgery, Harvard Medical School, Boston, MA, USA

* Corresponding author. Division of Otolaryngology, 45 Francis Street, Boston, MA 02115.
E-mail address: tcarroll@bwh.harvard.edu

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Abbreviations	
AAAAI	American Academy of Allergy, Asthma, and Immunology
BOS	Bronchiolitis obliterans syndrome
CC	Chronic cough
COPD	Chronic obstructive pulmonary disease
GERD	Gastroesophageal reflux disease
HEMII-pH	Hypopharyngeal-esophageal multichannel intraluminal impedance with dual-PH sensor
HRM	High-resolution esophageal manometry
ILD	Interstitial lung disease
IPF	Idiopathic pulmonary fibrosis
LES	Lower esophageal sphincter
LPR	Laryngopharyngeal reflux
LPRD	Laryngopharyngeal reflux disease
MII-pH	Multichannel intraluminal impedance and pH monitoring
NHWS	National Health and Wellness Survey
PPI	Proton pump inhibitors
QoL	Quality of life
RCC	Refractory chronic cough
SSc	Systemic sclerosis
UACS	Upper airway cough syndrome
UCC	Unexplained chronic cough
UES	Upper esophageal sphincter

Cough is a normal, reflexive, voluntary or involuntary, protective event. It comprises part of the somatosensory system involving visceral sensation, a reflex motor response, and associated behavioral responses.[3] Conclusive evidence that vagal afferent nerves are responsible for initiating the cough reflex has been provided. The originations of these vagal afferents are found in abundance in the airway mucosa and in the airway wall from the upper airways to the terminal bronchioles and lung parenchyma.[4] While cough fundamentally involves a neurologic reflex, there remains higher cortical control (eg, conscious inhibition/voluntary suppression and voluntary submission/induction). The motor pathways controlling voluntary and induced cough are nearly identical, so it is not easy to distinguish physiologically a cough that is voluntary from a cough that is a consequence of some visceral disease.[4] Laryngeal and tracheobronchial cough receptors, among others, respond to both mechanical and chemical stimuli (**Table 1**).

Chronic cough can have a detrimental impact on physical and mental health as well as unwanted socioeconomic consequences. It is associated with high utilization of health care resources involving multiple patient referrals, diagnostic tests, and drug prescriptions.[5] Compared to matched controls, those with chronic cough in the 2018 NHWS had *decreased* employment rate, number of college degrees, regular exercise, household income, healthy BMI, quality of sleep, total work productivity, general health-related quality of life (QoL) scores, and *increased* rates of anxiety/depression in the prior 2 weeks, sleep apnea, insomnia, narcolepsy, impairment in daily activities, and absenteeism at work. Higher rates of specialty visits to pulmonology, gastroenterology, and allergy as well as emergency room visits and hospitalizations highlight the degree of health care utilization within this population.[2]

As many as 50% of patients with CC are treated with opiates or other narcotics – a pressing concern given that overreliance on opioids is a driving factor of the opioid crisis.[5] Eighty patients with CC compared to matched controls in the UK demonstrated that the health care burden was nearly 3 times higher over the previous 5-

Table 1
Properties of vagal afferent nerve subtypes innervating the airways

Properties	Rapidly Adapting Receptors	Slowly Adapting Receptors	C-Fibers
Electrophysiologic			
Conduction velocity, m/s	14–23	15–32	0.8–1.5
Myelination	Yes	Yes	No
Eupneic activity, impulses/s	0–20	10–40	0.3–1.5
Morphologic			
Neuropeptide synthesis	No	No	Yes
Innervation of large airways[b]	Yes	Sparse	Yes
Innervation of small airways	Yes	Yes	Yes
Physical sensitivity			
Mechanical threshold	Low	Low	High
Lung deflation[a]	Activated	Inactivated	No effect
Edema	Increased	No effect	Increased
Chemical sensitivity[a]			
CO_2	No effect	Decreased	Increased
H^+	Increased	No effect	Increased
Capsaicin[a]	Increased[b]	No effect	Increased[c]
Bradykinin[a]	Increased[b]	No effect	Increased[c]
Reflex effects			
Parasympathetic	Excitatory	Inhibitory	Excitatory
Respiratory	Hyperpnea	Inhibit inspiration	Apnea
Axon reflex	No	No	Yes

[a] Typical attributes of the afferent nerve subtypes are listed. Species differences and subtypes of each class with distinct physiologic properties and responsiveness have been reported.
[b] The activation of RARs by capsaicin and bradykinin is prevented by *bronchodilator* pretreatment, suggesting that activation occurs secondary to obstruction in the lung.
[c] C-fiber activation by bradykinin and capsaicin is enhanced by bronchodilators such as adrenaline, adenosine, and *prostaglandin E*, suggesting that agents directly stimulate C-fibers in the airways. See text for further details and references.

Brendan J. Canning, Anatomy and Neurophysiology of the Cough Reflex: ACCP Evidence-Based Clinical Practice Guidelines, Chest, 129 (1), Supplement, 2006, 33S-47S, https://doi.org/10.1378/chest.129.1_suppl.33S.

year period. The mean number of visits to specialties managing CC was 9.3, compared to 1.1 for matched controls, and the annual mean number of visits to primary care was 10.4, compared to 6 for matched controls.[6]

There remains an unmet need for more effective CC management minimizing unnecessary steps and treatments.

DEFINITIONS

Refractory Chronic Cough and Unexplained Chronic Cough

Refractory chronic cough (RCC) and unexplained chronic cough (UCC) have been used interchangeably in numerous studies. While related, there remains a subtle but important difference between these 2 terms. Refractory chronic cough is a CC that persists despite guideline-based treatment, primarily treatment of "*The Big 3*": upper

airway cough syndrome (UACS), asthma (many now include non-asthmatic eosinophilic bronchitis), and reflux. This can be interpreted as *any* therapeutic trial for each of these 3, *or* after an exhaustive workup for each, including test/retest strategies to confirm adequate treatment of the disease being targeted, and therefore, assurance that the cough symptom is not due to these etiologies. In some studies, the definition of RCC has been extended beyond ruling out the 3 primary etiologies to include other known causes such as neurogenic cough, iatrogenic, and somatic cough syndrome.

The extent to which clinicians work up the 3 main causes before designating the cough as RCC is variable. For example, methacholine challenge is not always performed in patients who are not responsive to β-agonists. Similarly, reflux is often considered to be an acid-only problem, and ruling out reflux is incompletely accomplished through proton pump inhibitors (PPI) trials or pH-only testing. Because nonacidic reflux is not yet fully understood (or even accepted) by many cough-treating specialists, it becomes evident that ruling out the primary causes of CC is incomplete.

It is important to distinguish between cough that is truly unexplained (UCC) and cough that *can* be explained and treated effectively with additional interventions (RCC). Therefore, UCC is a *diagnosis of exclusion* (cough without any identifiable cause after applying the most up-to-date principles in CC management). According to the American College of Chest Physicians, UCC should not be made until (1) a thorough diagnostic evaluation is performed, (2) specific and appropriate treatment (according to the management protocols from the best literature) has been tried and has failed, and (3) *uncommon* causes have been ruled out.[7]

CURRENT EVIDENCE

Reflux

Gastroesophageal reflux disease (GERD) and laryngopharyngeal reflux disease (LPRD) can both be the primary trigger for a cough with refluxate targeting the esophagus, hypopharynx, larynx, oropharynx, nasopharynx, trachea, distal airways, and perhaps even the nasal passages since cough receptors are known to exist in each of these anatomic subsites (**Fig. 1**). For this reason, the term "reflux" will be used hereafter unless LPRD or GERD is specifically being discussed in the context of RCC.

Reflux induced cough should be considered in every case when cough has not responded to previous treatment trials for pulmonary and sinonasal etiologies, and prior to arriving at the diagnosis of RCC. The decision to treat reflux empirically or to test first is determined based on clinical judgment, availability of testing modalities in the local community, and shared decision making with the patient. While the majority of patients are told they do not have reflux as the cause of their cough through PPI trials and pH-only reflux testing, reflux cannot be eliminated definitively as a potential cause of RCC without multichannel intraluminal impedance and pH monitoring (MII-pH) testing using catheters that include two pH sensors [upper: at or slightly above the upper esophageal sphincter (UES) and lower: above the lower esophageal sphincter (LES)] and impedance sensors in the proximal esophagus and hypopharynx. This specialized MII-pH testing is called HEMII-pH (hypopharyngeal-esophageal multichannel intraluminal impedance with dual-PH sensor). If a more GERD-centric MII-pH catheter is used where impedance electrodes only go to 17 cm above the LES, the presence of hypopharyngeal non-acidic reflux events can be missed in the setting of what would be designated as an unremarkable examination.

Additionally, reflux should be considered when laryngeal penetration/aspiration is suspected (or confirmed) particularly in absence of cough when swallowing food and liquids.

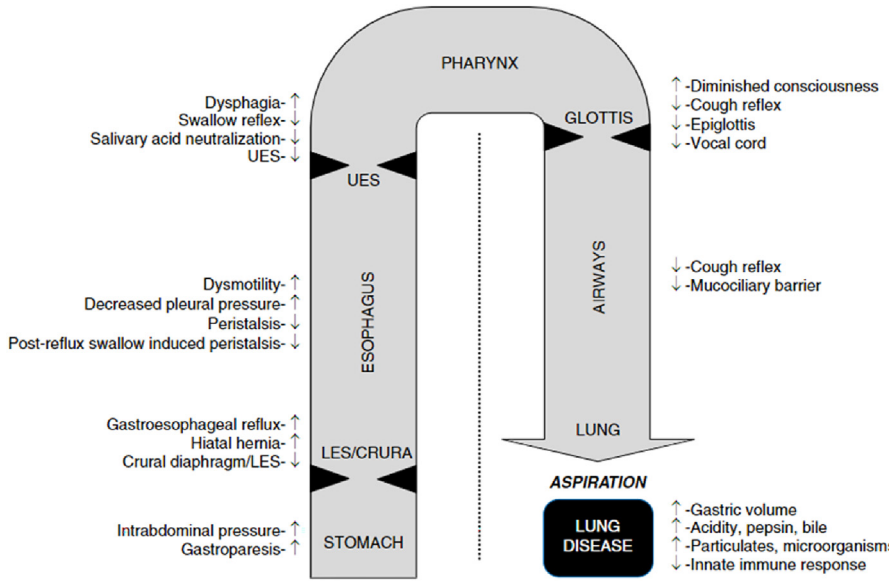

Fig. 1. Gastric-to-pulmonary aspiration. Although gastroesophageal reflux is prevalent, failure of multiple defense mechanisms is required for refluxate to reach the lower airways. The up arrows indicate items that favor or promote aspiration; the down arrows indicate mechanisms that protect against aspiration and its consequences. LES, lower esophageal sphincter; UES, upper esophageal sphincter. (Augustine S. Lee, Jay H. Ryu, Aspiration Pneumonia and Related Syndromes, Mayo Clinic Proceedings, 93 (6), 2018, 752-762, https://doi.org/10.1016/j.mayocp.2018.03.011.)

The following pearls can aid the clinician in achieving optimal reflux control to treat RCC resulting from reflux.

1. Acid reflux *and* non-acid reflux components (eg, pepsin, bile salts and other digestive enzymes) contribute to upper airway inflammation.
2. An immediate cause-and-effect relationship between laryngopharyngeal reflux (LPR) and cough is less commonly found on HEMII-pH testing. Therefore, a negative symptom correlation during HEMII-pH cannot exclude reflux as a contributor to cough.[8]
3. Esophageal dysmotility and delayed gastric emptying can add to the clinical picture and should be treated concomitantly in refractory cases.[3]
4. Nocturnal acid breakthrough and obstructive sleep apnea when identified should be included in the treatment plan.[9,10]
5. Eosinophilic esophagitis treatment including "2-4-6" diet elimination trials may prove beneficial in RCC patients. This includes a gluten free diet trial, among others.[11,12]
6. Anti-reflux surgery may be necessary to achieve cough resolution in patients with chronic cough due to reflux.[13]

24 Hour Hypopharyngeal-Esophageal Multichannel Intraluminal Impedance with Dual-pH Sensor Testing, Reflux, and Cough

Of 314 symptomatic patients who underwent HEMII-pH testing, 49 patients had chronic cough and only 52% had objective findings of GERD on endoscopy. Of 16 patients with abnormal proximal impedance exposure who subsequently underwent

anti-reflux surgery, 81% had resolution of cough and 19% had significant improvement at a median follow-up of 4.6 months.[13]

Manual analysis of proximal esophageal and pharyngeal events during HEMII-pH can avoid a false positive rate of 39.8% seen with automated analysis.[14] Manual reading provides a more accurate assessment of the symptom index and symptom association probability values for cough and other symptoms. Acoustic cough recording has been shown to be superior to patient symptom reporting during HEMII-pH as well.[15]

High-Resolution Esophageal Manometry, Esophageal Dysmotility, Reflux and Cough

High-resolution esophageal manometry (HRM) should be considered routinely with reflux testing in evaluation of patients presenting with suspected LPR.[16] Esophageal dysmotility can cause symptoms attributed to reflux in many patients.[17] High-resolution manometry revealed changes to UES function and esophageal motility in patients with chronic cough associated with impaired bolus clearance.[18]

Nuclear Imaging of Reflux and Cough

Van der Wall and colleagues developed a novel scintigraphic test to detect esophageal and extra-esophageal reflux events permitting direct visualization of refluxate in the upper aerodigestive tract and lungs.[19] Their work demonstrated reduction or resolution of LPR and pulmonary microaspiration using this visualization technique before and after laparoscopic fundoplication (**Fig. 2**A, B). More studies are needed to better understand its value in reflux management.

PULMONARY DISEASE AND REFLUX

The association between reflux and pulmonary disease has been studied extensively. In a respiratory health survey cohort, GERD was associated with increased asthma and bronchitis symptoms and exacerbations of respiratory symptoms.[20] Johnson and colleagues found that patients with typical symptoms of GERD also frequently have respiratory symptoms. In their series of patients who received open Nissen fundoplication for typical symptoms of GERD, 76% of those patients who also had respiratory symptoms experienced relief of those symptoms.[21]

Reflux and Asthma

The prevalence of reflux in the asthma population has been documented to be between 30% and 80%.[22] Several studies found that esophageal acid infusion can induce bronchoconstriction and cough reflex hypersensitivity in patients with asthma.[23] Microaspiration of refluxate is hypothesized to exacerbate asthma as well. The American Academy of Allergy, Asthma, and Immunology (AAAAI) states that asthmatics are at higher risk of developing reflux due to relaxation of the LES and medications like theophylline, while reflux can make asthma symptoms worse by irritating the airways and lungs.[24] AAAAI recommends treatment of reflux to help control asthma symptoms based on available studies.

Acid suppression therapy with omeprazole for 3 months improved asthma symptoms and peak expiratory flows by morer than 20% and improved pulmonary function in 73% of asthmatics with GERD.[25] Esomeprazole 40 mg daily or twice daily resulted in minor improvements in asthma related QoL and pulmonary function tests.[26] PPI alone did not improve asthma control, QoL, or lung function in patients with

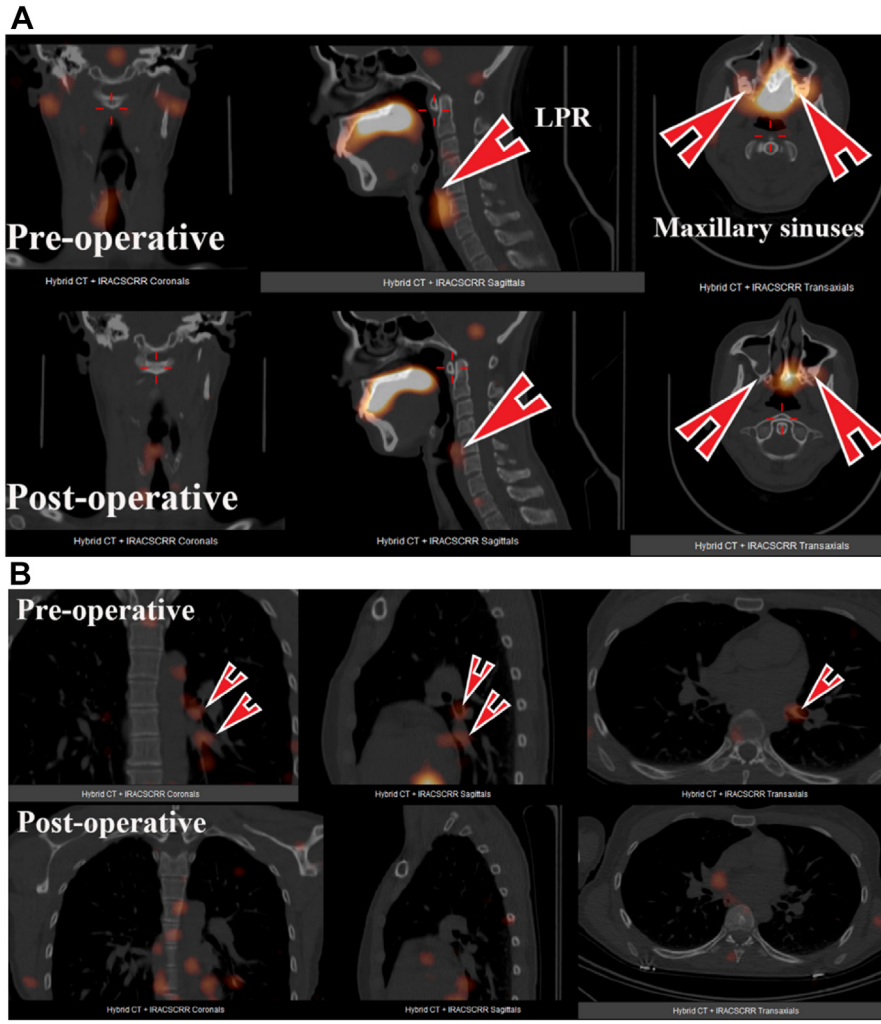

Fig. 2. (*A*) Single-photon emission computed tomography/computed tomography (SPECT/CT) illustration of the response to laparoscopic fundoplication with significant decrease in the volume of gastroesophageal reflux showing significant reduction in the degree of contamination of both the laryngopharynx and the nasal cavities. (*B*) SPECT/CT imaging of the lungs demonstrating the reversal of pulmonary microaspiration into the left lower lobe bronchus following laparoscopic fundoplication. Note contamination of the blood pool in the heart from tracer breakdown. (Van der Wall, H., Burton, L., Cooke, M., Falk, G.L., Tovmassian, D. and Conway, J.J. (2025), Scintigraphic Imaging of Extra-Esophageal Manifestation of Gastresophageal Reflux Disease. The Laryngoscope, 135: 73-79. https://doi.org/10.1002/lary.31748.)

GERD.[27] Because of the effects of non-acid reflux and microaspiration, acid suppression alone may not be the optimal approach to reflux management in asthmatics.

Reflux and Chronic Obstructive Pulmonary Disease

Reflux is associated with a higher chance of experiencing acute exacerbations of chronic obstructive pulmonary disease (COPD).[28]

Some proposed mechanisms explaining COPD *causing* reflux include obesity, poor health/functional status, increased IL-6, decreased neutrophils, decreased saliva, hypotensive UES and LES pressures,[29] hypoxia, and medications (beta agonists[30] and anticholinergics[31]) to treat COPD. The crural diaphragm is an extrinsic sphincter on the lower esophagus. Flattening of the diaphragm induced by pulmonary hyperinflation in COPD has been suggested to influence hypotensive LES pressure.[32]

Proposed mechanisms for reflux *causing* COPD include microaspiration and lung injury with pepsin identified in the lungs. Increased COPD exacerbations have been associated with higher prevalence of reflux.[33] Studies suggest that patients with COPD have a poor bronchoconstrictive reflex to distal esophageal reflux based on acid infusion trials.[34] COPD patients with reflux also showed increased progression of air trapping on CT.[35]

Reflux and Interstitial Lung Disease

Reflux has been proposed as a contributing factor in the pathogenesis of interstitial lung disease (ILD) especially idiopathic pulmonary fibrosis (IPF) and systemic sclerosis. Microaspiration over time can lead to pneumonitis, increased epithelial permeability, stimulation of fibrotic proliferation, and eventual lung fibrosis.[36] Pepsin levels on BAL were higher in patients with ILD and chronic cough compared to lung cancer controls.[37] Early treatment of reflux, therefore, may prevent progression and detrimental effects on lung disease exacerbation in ILD due to aspiration of gastric contents.

GERD was present in 94% of systemic sclerosis (SSc) patients and in 96% of those with SSc-ILD.[38] Combination therapy with a PPI *and* histamine-2 receptor antagonist was associated with a greater survival benefit than with PPI alone in this study.

GERD and hiatal hernia are common comorbidities in patients with IPF, a subtype of ILD. Estimates suggest that 30%–50% of those with IPF also experience GERD.[39] Trials have been conducted to explore the use of reflux therapy in slowing the progression of IPF, but the results remain inconclusive.[40] Anti-reflux surgery for IPF has shown success in individuals awaiting lung transplants.[41] Significant improvement in transplant-free survival in IPF was seen with pharmacologic reflux treatment.[42]

The American Thoracic Society 2022 IPF guidelines did not recommend reflux treatment to improve respiratory function, but it remains indicated for those with reflux symptoms.[43]

Reflux and Lung Cancer

According to a population-based cohort study of 42,555 people, GERD patients had a higher prevalence of lung cancer than healthy controls.[44] Patients with non-small cell lung cancer have significantly higher rates of GERD than the general population.[45] In another multinational cohort study, patients who had anti-reflux surgery had a lower risk of developing small cell and squamous-cell lung carcinoma.[46]

Reflux and Bronchiolitis Obliterans

Bronchiolitis obliterans syndrome (BOS) is one of the most common noninfectious complications in lung transplant recipients. Reflux with microaspiration has been shown to increase the risk of developing BOS after lung transplantation, and anti-reflux surgery can positively influence the course of the transplant over time.[47,48]

SUMMARY

Reflux treatment is important to optimize management of respiratory diseases including chronic cough, asthma, COPD, ILD, and lung transplantation. For definitive

evaluation of reflux, testing with HEMII-pH and HRM is an important step. A treatment plan addressing *all* reflux contents (acid and non-acid) will yield the highest success compared to treatment of acid reflux alone. Multi-modality reflux treatment and/or anti-reflux surgery along with shared decision making can improve outcomes in many patients with concomitant reflux and respiratory disease.

CLINICS CARE POINTS

- Reflux is an important cause of chronic cough.
- Patients with RCC should be evaluated for reflux with HEMII-pH and HRM.
- Effective treatment of reflux can improve outcomes in many pulmonary diseases such as asthma, COPD, ILD, and following lung transplantation.
- Treatment of reflux in the management of respiratory diseases should address acid and non-acid reflux with multimodality therapy and/or anti-reflux surgery.

DISCLOSURES

T.L. Carroll is a consultant for Pentax Medical, Ambu and GSK. He has received stock options from and is on the scientific advisory board for Sofregen Medical and N-Zyme Biomedical. He receives royalties from Plural Publishing. A.J. Jaworek is a consultant for Smith + Nephew.

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