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# Gluten Sensitivity

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**G**LUTEN SENSITIVITY CAN BE A PROBLEM FOR SINGERS. Singing teachers should suspect it in patients who have what appears to be uncontrolled reflux symptoms despite appropriate reflux treatment, especially in students who develop bloating or diarrhea after consuming pasta, wheat bread, and other foods associated with hypersensitivity. Teachers should not hesitate to recommend medical evaluation when intolerance is suspected.

Diagnoses represented within the gluten sensitivity spectrum are as diverse and nebulous as are its presenting symptoms, as we have discussed elsewhere and are reviewing here.<sup>1</sup> One of the best categorizations found in the recent literature subdivides gluten sensitivity into allergic, autoimmune, and nonallergic/nonautoimmune, or simply immune.<sup>2</sup> The allergy category includes wheat allergy (WA) or food allergy, wheat-dependent exercise-induced anaphylaxis (WDEIA), occupational or Baker's asthma, and contact urticaria. The autoimmune category includes celiac disease (CD), dermatitis herpetiformis, and gluten ataxia. Nonceliac gluten sensitivity (NCGS) belongs to the third category, which is the newest and least studied but also the most intriguing. The scientific community is just beginning to recognize the existence of NCGS as a disease with distinct pathophysiologic and epidemiologic characteristics. While the prevalence of CD in the United States is between 0.5–1%,<sup>3</sup> epidemiologic studies place NCGS prevalence in the United States slightly higher, with best estimates ranging from 0.55 to 6%.<sup>4</sup>

Gluten sensitivity including CD and NCGS presents with gastrointestinal and extra-intestinal symptoms. The most common GI complaints include irritable bowel syndrome (IBS)-like symptoms (e.g., bloating, abdominal pain, bowel habit abnormalities such as diarrhea and/or constipation), and even symptoms of GERD (heartburn and regurgitation).<sup>5</sup> For example, between 2004 and 2010, 5,896 patients were seen at the Center for Celiac Research, University of Maryland.<sup>6</sup> The criteria for gluten sensitivity were fulfilled by 347 (6%) of the patients seen. Their symptoms included abdominal pain (68%); eczema and/or rash (40%); headache (35%); "foggy mind" (34%); fatigue (33%); diarrhea (33%); depression (22%); anemia (20%); numbness in the legs, arms, or fingers (20%); and joint pain (11%). Other studies have confirmed these symptoms in this population.<sup>7</sup> Gluten sensitivity, particularly CD, also has been associated with an increased risk of other autoimmune disorders such as autoimmune thyroiditis, type I diabetes mellitus, Addison disease, Crohn's and ulcerative colitis, myasthenia gravis, and psoriasis.<sup>8</sup> It is equally important to recognize that some of these patients have minimal or no

symptoms, making it even more difficult to select those who would benefit from a diagnostic workup. Fasano et al. found that 41% of patients with positive serology for CD were asymptomatic.<sup>9</sup> This problem is compounded further by the nonspecific nature of extra-intestinal symptoms, the variable effect of gluten on an individual's immune system, the observation that many patients are already on a gluten free diet (GFD) or a low fermentable oligo-di-monosaccharides and polyols (FODMAP) diet at the time of presentation, and the possibility that other extra-intestinal symptoms may be linked but not yet identified. It is conceivable, given the current evidence linking gluten sensitivity with GERD, which the signs and symptoms attributed to laryngopharyngeal reflux (LPR) also might be linked to gluten sensitivity in this population, but this possibility has not been studied.

At the present time, there are insufficient data linking CD and NCGS with laryngopharyngeal reflux (LPR). Conversely, studies have identified that the esophagus is not spared in patients with gluten sensitivity. Consistent data are now available on the presence of disturbed motility of the esophagus, along with the stomach, small intestine, gallbladder, and colon of untreated patients with CD.<sup>10</sup> Using esophageal manometry, Usai et al. studied the presence of specific esophageal motor disorders in this population.<sup>11</sup> They reported motor abnormalities in 67% of 18 patients with CD. They consisted of nutcracker esophagus (50%), low pressure in LES associated with simultaneous contractions (11%), and frequent repetitive contractions (22%). No subjects in the control group (34 patients) and the ulcerative colitis group (9 patients) had these manometric abnormalities. Additional interesting findings in the study group were the presence of dysphagia in 50% (vs. 9% of controls) and odynophagia in 14% (vs. 0% of controls) of 36 patients with CD.

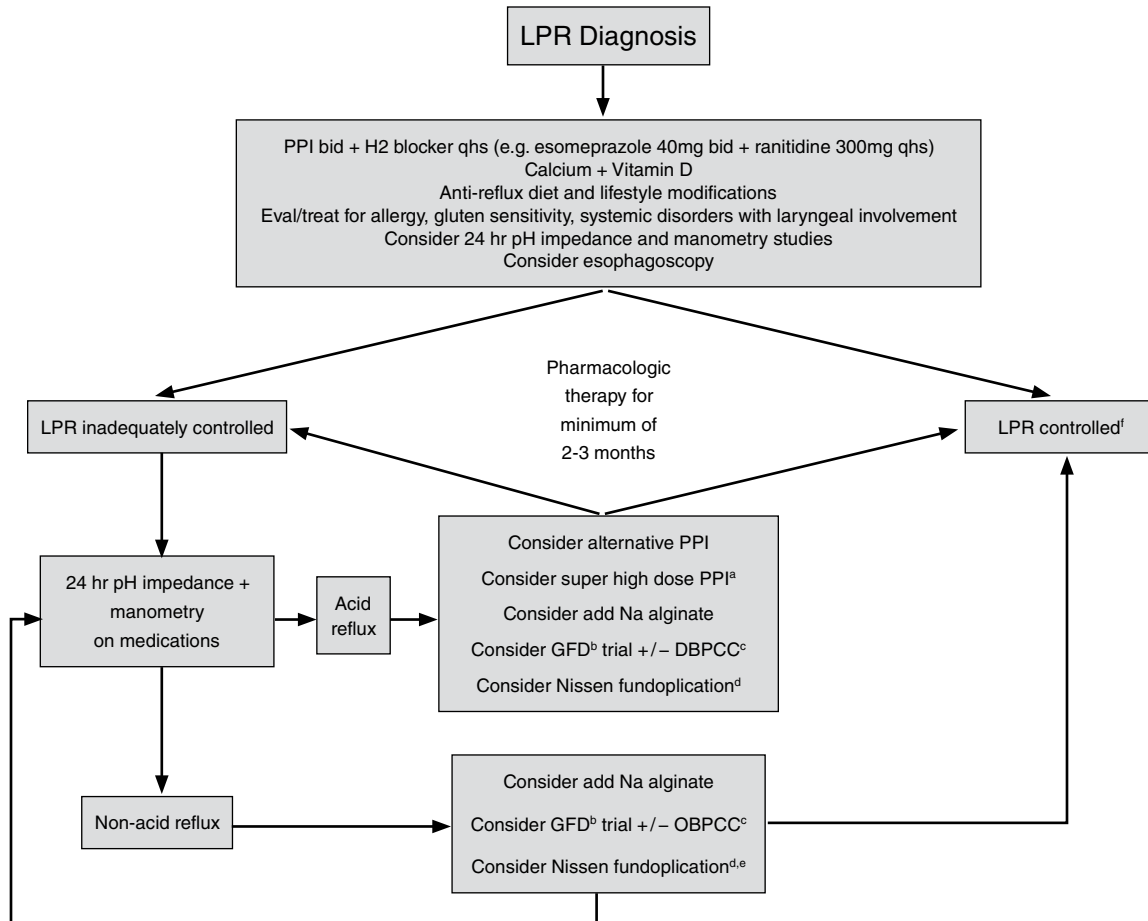
There have been studies exploring GERD in the gluten sensitive population, primarily those with CD. The findings show that GERD symptoms are more common in patients with CD than in the general population. In a study by Nachman et al., 30% of patients complained of moderate to severe GERD symptoms at the time of CD diagnosis (defined as score >3 in the Gastrointestinal Symptoms Rating Scale),<sup>12</sup> a rate 6-fold higher than the rate seen in healthy controls (5.7%).<sup>13</sup> A gluten free diet (GFD) has been shown to improve symptoms of GERD in

patients with CD, irrespective of PPI therapy.<sup>14</sup> Because GERD-like symptoms can be a presentation of active celiac disease and nonceliac gluten sensitivity, some studies have concluded that celiac disease should be considered, and investigated, by means of serology or with duodenal biopsies during EGD, in patients with refractory GERD, especially if these patients exhibit other signs or symptoms suggestive of CD.<sup>15</sup> Although Collin et al. argued against screening for CD in patients with reflux esophagitis, concluding that GERD is not a major manifestation of CD, they also commented that a GFD may result in symptomatic relief of reflux symptoms in patients with CD.<sup>16</sup> The study also did not explore this question in patients with NCGS.

A study by Lamanda et al. documented esophageal erosive lesions in 23% of 65 adult patients diagnosed with CD over a year, a prevalence far above that which was established for the general population.<sup>17</sup> Cuomo et al. monitored esophageal pH in 15 out of the 39 celiac patients included in their case series; 14 out of 15 showed pathologic pH levels. Furthermore, lower esophageal sphincter (LES) pressure values trended lower than those observed in healthy controls, although the differences did not reach statistical significance.<sup>18</sup>

There is interesting literature illustrating the relationship that exists between GERD and GFD in patients with CD. A GFD alone reduces severity of both heartburn and regurgitation significantly in adults with CD.<sup>19</sup> In patients with CD treated with PPI, a GFD also reduced the risk of recurrence of GERD-related symptoms after discontinuation of antisecretory treatment. Nachman et al. found that after 3 months from the start of the GFD, GERD-related symptom scores had decreased significantly in their series of adult patients with CD, reaching values similar to those of healthy controls.<sup>20</sup> Lamanda et al. showed that GERD symptoms had remitted in 91% of adult patients with CD after 4 weeks of treatment with PPI at standard doses, with no relapse in any case after 12 months of follow-up on GFD.<sup>21</sup> A GFD also has been shown to prevent recurrence of GERD-related symptoms in patients with CD who have both erosive and nonerosive esophagitis.<sup>22</sup> Long term benefit of a GFD on GERD symptoms still persist in the event of partial compliance.<sup>23</sup>

The potential association between laryngopharyngeal reflux (LPR) and gluten sensitivity was not investigated

**Table 1.** Laryngopharyngeal reflux algorithm incorporating gluten sensitivity evaluation and management.

- a) J.E. Portnoy, N.D. Gregory, C.E. Cerull, et al., "Efficacy of super high dose proton pump inhibitor administration in refractory laryngopharyngeal reflux: A pilot study," *Journal of Voice* 28, no. 3 (May 2014): 369–377.
- b) Gluten free diet may be considered at any step in the pathway with serologic testing recommended prior to initiation.
- c) DBPCC = Double Blind Placebo Controlled (gluten) Challenge.
- d) Repeat 24 hr pH Impedance with manometry off antisecretory medications is recommended 3 months post-Nissen fundoplication.
- e) Nissen fundoplication is likely to be therapeutic for nonacid reflux laryngitis, especially if a positive symptom index during 24 hr pH impedance testing.
- f) Nissen fundoplication should be considered for patients who do not want to use antisecretory medications long term.

until our (RTS) preliminary study. In our practice, this connection has become more apparent after a growing number of patients have reported improvement in symptoms usually associated with LPR while following a gluten free diet (GFD).

Numerous mechanisms have been proposed to explain the association of gluten sensitivity and GERD. In summary, they have included nutrient malabsorp-

tion affecting gastroesophageal motility, GI hormonal derangements causing decreased LES pressures and dysmotility, and the inflammatory reaction to gluten resulting in increased mucosal permeability.<sup>24</sup> Wex et al. report that zonulin, a protein involved in the regulation of interepithelial permeability in the intestines of CD patients, may be implicated since it was found to be expressed in esophageal epithelial cells, as well.<sup>25</sup> In

**TABLE 2.** Laboratory evaluation of gluten sensitivity (CD=Celiac Disease; NCGS =non celiac gluten sensitivity).

Lab Test	Can test on gluten-free diet?	Indication	Sensitivity	Specificity
Tissue Transglutaminase (TTG)				
TTG IgA	no	Celiac disease	98%	98%
TTG IgG	no	Celiac disease	70%	95%
Deamidated Gliadin Peptide (DGP)				
DGP IgA	no	Celiac disease	88%	95%
DGP IgG	no	Celiac disease	80%	98%
Anti-gliadin Antibody (AGA)				
AGA IgA	no	Celiac disease	85%	90%
AGA IgG	no	Celiac disease/NCGS	85% (CD)	80% (CD)
Endomysial Antibody IgA	no	Celiac disease	95%	99%
Wheat specific IgE	no	Wheat llerqy (IqE)	83%	43%
HLA DQ2 and DQ8	yes	Celiac disease/NCGS	rv100% (CD)	low; varies depending on population

addition to these potential mechanisms, Tursi also has proposed the possible involvement of neurotransmitters and the direct toxic effect of gluten on muscular tissues.<sup>26</sup> In a similar manner, one or more of these potential mechanisms could contribute to the presence of LPR in these patients.

Tursi reported on 3 patients with GERD refractory to antisecretory treatment who were diagnosed with CD after duodenal biopsies and who had rapid and long lasting remission of symptoms after starting a GFD.<sup>27</sup> In one example; a 24 year old woman had persistent GERD symptoms despite esomeprazole 80 mg/day. Twenty days after starting PPI therapy, celiac disease was diagnosed based on histologic evaluation, and the patient was started immediately on a GFD. Symptoms improved within 7 days and disappeared completely within 2 weeks of GFD despite cessation of PPI therapy, and she remained symptom free 6 months later.

Lucendo acknowledged this observation by stating that the lack of response to PPI therapy to improve GERD symptoms, even after increasing the doses, could be the key for suspecting and actively excluding CD.<sup>28</sup> Regardless of the pathophysiology of GERD symptoms in patients with CD, the question arises whether GFD should be added to antisecretory treatment, since it appears that symptom improvement may be more related in these patients to gluten suppression than to

medication. In his editorial, Tursi proposed avoiding antisecretory medications altogether and instead using antacids such as sodium alginate to treat nonerosive GERD in patients with CD until gluten elimination reversed clinical symptoms.<sup>29</sup>

The current literature has shown that GERD is more prevalent in patients with CD and that it responds favorably to GFD. Pending future studies, a similar observation is likely to be established between GERD and NCGS. The impact of gluten sensitivity on LPR, however, represents a new frontier of untapped research potential. From our clinical observations and identifications of current gaps in existing knowledge, it can be concluded that further research investigating this potential relationship is warranted. We have incorporated consideration for possible gluten sensitivity into our routine assessment of patients with suspected LPR (Table 1).

At a minimum, the knowledge presented here should prove useful for laboratory screening and referring patients to our gastroenterology colleagues if suspicion for gluten sensitivity arises. Following the most recent literature and national guidelines on CD and NCGS including the American College of Gastroenterology (ACG),<sup>30</sup> our practice has initiated laboratory testing for patients with LPR, particularly when refractory to antisecretory reflux therapy or when indicated by the

patient's history. This laboratory panel includes the following:

- tissue transglutaminase (TTG) IgA, IgG
- deamidated gliadin peptide (DGP) IgA, IgG
- anti-gliadin antibody (AGA) IgA, IgG
- total IgA
- wheat specific IgE
- HLA-DQ genotyping

Some laboratories have incorporated reflex testing into their celiac disease panels to look for tissue transglutaminase IgG if total IgA is low, for example, since 2–3% of patients with celiac disease also have IgA deficiency. HLA DQ2 or DQ8 is present in nearly 100% of patients with celiac disease, while it is present in 50% of patients with NCGS and 30–40% of the general population. This test, along with AGA IgG (positive in 56% of patients with NCGS), presently are the only 2 commercially available laboratory tests that have been shown to be positive more often in NCGS patients than in the general population. Algorithms have been developed to help guide evaluation and workup,<sup>31</sup> and our approach is summarized in Table 2. If CD is diagnosed or if NCGS is suspected, a GFD trial may be recommended, along with referrals to a gastroenterologist and a nutritionist.

## NOTES

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