

Low-Acid Diet for Recalcitrant Laryngopharyngeal Reflux: Therapeutic Benefits and Their Implications

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Objectives: Laryngopharyngeal reflux (LPR) is an expensive, high-prevalence disease with a high rate of medical treatment failure. In the past, it was mistakenly believed that pepsin was inactive above pH 4; however, human pepsin has been reported to be active up to pH 6.5. In addition, it has been shown by Western blot analysis that laryngeal biopsy samples from patients with symptomatic LPR have tissue-bound pepsin. The clinical impact of a low-acid diet on the therapeutic outcome in LPR has not been previously reported. To provide data on the therapeutic benefit of a strict, virtually acid-free diet on patients with recalcitrant, proton pump inhibitor (PPI)-resistant LPR, I performed a prospective study of 20 patients who had persistent LPR symptoms despite use of twice-daily PPIs and an H₂-receptor antagonist at bedtime.

Methods: The reflux symptom index (RSI) score and the reflux finding score (RFS) were determined before and after implementation of the low-acid diet, in which all foods and beverages at less than pH 5 were eliminated for a minimum 2-week period. The subjects were individually counseled, and a printed list of acceptable foods and beverages was provided.

Results: There were 12 male and 8 female study subjects with a mean age of 54.3 years (range, 24 to 72 years). The symptoms in 19 of the 20 subjects (95%) improved, and 3 subjects became completely asymptomatic. The mean pre-diet RSI score was 14.9, and the mean post-diet RSI score was 8.6 ($p = 0.020$). The mean pre-diet RFS was 12.0, and the mean post-diet RFS was 8.3 ($p < 0.001$).

Conclusions: A strict low-acid diet appears to have beneficial effects on the symptoms and findings of recalcitrant (PPI-resistant) LPR. Further study is needed to assess the optimal duration of dietary acid restriction and to assess the potential role of a low-acid diet as a primary treatment for LPR. This study has implications for understanding the pathogenesis, cell biology, and epidemiology of reflux disease.

Key Words: acid reflux, adenocarcinoma, antireflux, Barrett's esophagus, chronic cough, diet, esophageal cancer, gastroesophageal reflux disease, heartburn, hoarseness, laryngopharyngeal reflux, low acid, low fat, pepsin, proton pump inhibitor.

INTRODUCTION

Laryngopharyngeal reflux (LPR) is a controversial, high-prevalence disease, and it differs from classic gastroesophageal reflux disease (GERD) in many ways.¹⁻¹⁰ Typically, patients with LPR have daytime (upright) reflux without having heartburn or esophagitis.¹⁻³ In addition, one of the most important differences between LPR and GERD is that the threshold for laryngeal tissue damage is much lower than that for the esophagus.^{1,5,8} As many as 50 reflux episodes (less than pH 4) per day are considered normal for the esophagus, whereas as few as 3 reflux episodes per week are too many for the larynx.¹

THERAPEUTIC IMPLICATIONS OF CELL BIOLOGY OF LPR

The cell biology of LPR holds the key to understanding the susceptibility of the larynx to peptic in-

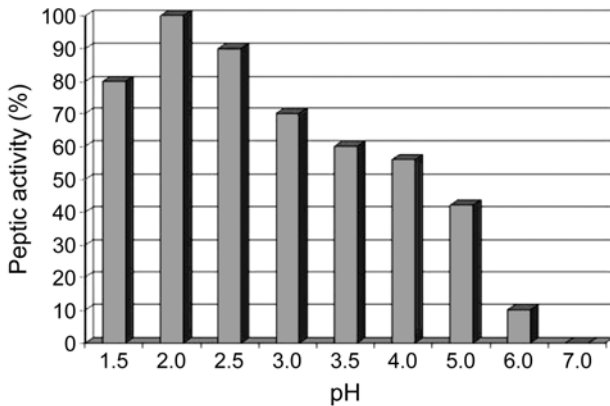
jury — and it is peptic (not acid) injury.^{1,5,8,9,11-17} (Pepsin does, however, require some acid for activation.) We previously showed that 19 of 20 patients (95%) with clinical and pH-documented LPR had tissue-bound pepsin identifiable by Western blot analysis, as opposed to only 1 of 20 control subjects (5%).⁹ In addition, peptic injury is associated with depletion of key protective proteins, including carbonic anhydrase, E-cadherin, and most of the stress proteins.^{5,8,9,11-15}

Equally important in understanding the biology of LPR is consideration for the stability and spectrum of activity of human pepsin.¹⁴ In the past, it was mistakenly believed that pepsin was inactive above pH 4.¹ The early experiments on which that result was based were performed with porcine pepsin, and not human pepsin. Indeed, pig pepsin is inactive at greater than pH 4; however, human pepsin retains some of its proteolytic activity up to pH 6.5,

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Presented at the meeting of the American Broncho-Esophagological Association, Las Vegas, Nevada, April 28-29, 2010.

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Human pepsin activity curve. (Data from Johnston et al.¹⁴)

depending on the substrate.¹⁴ The pepsin activity curve is shown in the Figure.¹⁴ Peak peptic activity (100%) occurs at pH 2, but there is still some (10%) activity at pH 6.¹⁴ In other words, clinical disease (LPR) is associated with tissue-bound pepsin,⁹ and laryngeal damage occurs at pH 5.0 or less.⁸

CLINICAL CONSIDERATIONS

For more than 25 years, LPR was diagnosed in my practice by the symptoms and findings of LPR and by ambulatory 24-hour (simultaneous pharyngeal and esophageal) pH monitoring.^{1-3,7} Treatment for moderate to severe LPR was typically twice-daily proton pump inhibitors (PPIs) with an H₂-receptor antagonist at bedtime and an antireflux dietary and lifestyle modification program (Table 1).

There was some customization of the conventional antireflux protocol, eg, one cup of coffee a day, no citrus, no carbonated beverages. We have long recognized that some patients who drank excessive amounts of carbonated beverages might gain control of their LPR simply by eliminating those beverages. Indeed, carbonated beverage consumption is one of the most common identifiable causes of medical treatment failure in LPR.

With our 2007 study¹⁴ showing peptic activity up to pH 6.5, and having previously found (by immunohistochemical analysis) pepsin within the tissue biopsy specimens of patients with LPR,⁹ we recognized that tissue-bound pepsin in these patients might be activated by exogenous hydrogen ions from any source, including dietary ones. Consequently, in 2008 we began measuring the pH of common foods and beverages and restricting patients with LPR from consuming anything below pH 5 for a trial period of 2 weeks. To our surprise, this appeared to have outstanding therapeutic benefits for many patients.

In the ensuing few years, we continued to refine

TABLE 1. TRADITIONAL ANTIREFLUX DIET AND LIFESTYLE MODIFICATION PROGRAM

If you use tobacco, quit, because smoking causes reflux.
Do not wear clothing that is too tight, especially trousers, corsets, and belts.
Avoid exercising, especially weight-lifting, swimming, jogging, and yoga, after eating.
Do not lie down after eating; do not eat within 3 hours of bedtime.
Elevate the head of your bed if you have nighttime reflux (hoarseness, sore throat, and/or cough in the morning).
Limit your intake of red meat, butter, cheese, eggs, and anything with caffeine.
Completely avoid fried food, high-fat meats, onions, tomatoes, citrus fruit or juice, carbonated beverages (soda), beer, hard liquor, wine, mints, and chocolate.

this *induction reflux diet* to exclude all recognized reflux trigger foods, as well as anything that we identified to be acidic (below pH 5). Eggs and red apples, for example, used to be on the induction diet, but we found that those foods caused problems for some of our patients, so they were removed. Thus, the approved foods and beverages list for the induction reflux diet evolved to its present form (Table 2).

MATERIALS AND METHODS

All of my adult patients with pH-documented LPR on “maximum” antireflux therapy (twice-daily PPIs with an H₂-receptor antagonist at night) were eligible for the study if they were failing to improve on medical treatment and did not have potentially life-threatening manifestations of LPR. Specifically excluded were patients with airway stenosis, laryngeal neoplasia, and/or pulmonary disease. Medical treatment failure was defined as no improvement in symptoms — according to a validated outcomes measure, the reflux symptom index (RSI)^{18,19} — on office visits at least 2 months apart. Incidentally, it has been my routine practice for the past 25 years to have all patients complete the RSI at every visit.

Before inclusion in the low-acid diet study, patients were offered other alternatives such as changing their antireflux medications or evaluation for antireflux surgery. If the low-acid reflux diet was elected (Table 2), patients had to agree to be compliant with the conditions of the diet, which was very restrictive (nothing below pH 5). For example, the diet allows no fruit except bananas and melons. Patients were counseled about what they could and could not eat and were provided with a handout that explained the purpose of the diet and its scientific basis, as well as a list of foods and beverages that were allowed. Study subjects were instructed to eat only from the list of the items in Table 2 for 2 weeks

TABLE 2. INDUCTION REFLUX DIET

Agave
Aloe vera
Artificial sweetener (maximum 2 teaspoons per day)
Bagels and (non-fruit) low-fat muffins
Banana (great snack food)
Beans (black, red, lima, lentils, etc)
Bread (especially whole grain and rye)
Caramel (maximum 4 tablespoons per week)
Celery (great snack food)
Chamomile tea (most other herbal teas are <i>not</i> acceptable)
Chicken (grilled, broiled, baked, or steamed; no skin)
Chicken stock or bouillon
Coffee (maximum 1 cup per day; best with milk)
Egg whites
Fennel
Fish (grilled, broiled, baked, or steamed)
Ginger (ginger root, powdered, or preserved)
Graham crackers
Herbs (excluding all peppers, citrus, garlic, and mustard)
Honey
Melon (honeydew, cantaloupe, watermelon)
Mushrooms (raw or cooked)
Oatmeal (all whole-grain cereals)
Olive oil (maximum 2 tablespoons per day)
Parsley
Pasta (with nonacidic sauce)
Popcorn (plain or salted, no butter)
Potatoes (all of the root vegetables except onions)
Rice (healthy, especially brown rice, a staple during induction)
Skim milk (alternatively, soy or Lactaid skim milk)
Soups (great homemade with noodles and vegetables)
Tofu
Turkey breast (organic, no skin)
Turnip
Vegetables (raw or cooked, but no onion, tomato, or peppers)
Vinaigrette (maximum 1 tablespoon per day; toss salads)
Whole-grain breads, crackers, and breakfast cereals

or until the first follow-up visit thereafter.

I performed a laryngeal examination with each office visit, as is the routine for management of LPR. The reflux finding score (RFS)²⁰ was calculated for each patient for each visit; however, for this study, it was not blinded, as it was anticipated that there would be no significant change in the RFS. We have previously reported that the laryngeal findings of LPR do not usually change as quickly as the symptoms.¹⁹ (I never expected the degree of improvement in the RFS that was found.) For statistical analysis I used Students' *t*-test for the pre-diet and post-diet RSI and RFS data.

Institutional Review Board approval was not sought for this study, as it was deemed unnecessary

because 1) the strict, low-acid, induction reflux diet carried no risk of harm; 2) the diet was a logical extension of the traditional antireflux diet; 3) alternative therapeutic alternatives were neither denied nor precluded; and 4) there was no risk of violation of patient confidentiality, as no one but the author had access to the study data.

RESULTS

There were 12 male and 8 female subjects with a mean age of 54.3 years (range, 24 to 72 years). All of the study subjects claimed complete compliance with the prescribed diet. Nineteen of the 20 subjects (95%) improved on the low-acid diet, and 1 got worse. Three subjects became completely asymptomatic, and another went from an initial RSI score of 28 to a post-diet RSI score of 4. The mean pre-diet RSI score was 14.9, and the mean post-diet RSI score was 8.6 ($p = 0.020$); the mean RSI improvement was 6.3. The mean pre-diet RFS was 12.0, and the mean post-diet RFS was 8.3 ($p < 0.001$). The data are shown in Table 3.

DISCUSSION

In 1981, I was emergently consulted to see a patient with airway obstruction. Portable endoscope in hand, I rushed to the hospital to see a stridorous patient. She calmly pointed to her throat and gasped, "Can't breathe...acid reflux." After a quick bedside endoscopy, I took her to the operating room and removed the two largest obstructing vocal process granulomas that I have ever seen before or since. The patient was placed on a postoperative regimen of high-dose cimetidine, head-of-bed elevation, and a restricted diet: no fried food, no coffee, no tomatoes, onions, garlic, cheese, chocolate, or mints, as well as no late eating. Under that treatment, the patient got well. She was my introduction to LPR.

In the 30 years since, reflux medications have evolved, and now many patients with LPR are started on "maximal antireflux treatment" consisting of twice-daily PPIs (before breakfast and before the evening meal) and an H₂-receptor antagonist at bedtime.²¹ Although this regimen results in better acid suppression than did previous medical therapy, there is still a significant rate of medical treatment failure (10% to 17%).^{22,23} It is presumed that PPI failure is due to a "bioavailability" problem (ie, poor drug absorption).²²

More than a decade ago, we recognized that carbonated beverages, particularly caffeinated cola drinks, were a major risk factor for LPR. Indeed, excessive consumption of carbonated beverages was the single most commonly identified cause of medical treatment failure among our patients with LPR.

TABLE 3. RESULTS

Subject	Age (y)	Sex	Reflux Symptom Index Score			Reflux Finding Score	
			Before Diet	After Diet	Change	Before Diet	After Diet
1	29	F	28	4	24	13	8
2	70	F	4	3	1	12	5
3	72	F	10	0	10	10	0
4	53	M	10	8	2	10	9
5	61	M	29	35	-6	12	12
6	41	M	18	15	3	13	10
7	62	M	20	8	12	11	9
8	57	M	1	0	1	10	4
9	82	F	2	0	2	14	9
10	33	M	12	10	2	14	11
11	65	M	27	16	11	16	11
12	52	F	21	12	9	14	9
13	63	M	13	7	6	9	5
14	60	M	7	4	3	9	9
15	60	F	7	3	4	12	11
16	59	M	19	7	12	11	10
17	52	F	21	16	5	14	11
18	24	M	22	9	13	12	11
19	39	M	15	8	7	12	8
20	52	F	12	7	5	12	4
Mean	54.3		14.9	8.6	6.3	12.0	8.3

On the basis of clinical experience, we also limited our patients' intake of citrus fruits and hot (pepper) sauces. Other than these few specifics, the antireflux diet has not changed much over the years — that is, until recently. In 2008, we began measuring the pH of common foods and beverages, and as a consequence of finding acid in almost everything we tested, we began to limit the acid intakes of our patients with LPR, with surprisingly good results.

The clinical results reported herein are particularly striking and significant because “maximum anti-reflux therapy” was failing in the study patients. In the months since this paper was presented, many additional patients with LPR have been treated with a low-fat, low-acid diet as the cornerstone of therapy, with or without adjunctive antireflux medications.

The induction reflux diet is still recommended for the first 2 to 4 weeks with a gradual reintroduction of some fatty foods and other historically “refluxogenic” foods. Cheese, eggs, meats, sauces, and condiments are allowed in moderation, but the key elements of the *maintenance reflux diet* are that it remains relatively low in acids and low in fat.

With fatty foods in particular, we teach patients moderation, and to use tasty fats as flavorings, not as main ingredients. We also introduce the concept of pH balancing. The idea is that acidic foods may be combined with nonacidic foods. Strawberries, for example, which are not allowed to be eaten by

themselves on the reflux diet, are permitted when added to breakfast cereal with milk, preferably low-fat milk, which has a high pH. In other words, the cereal and milk buffer the acidic fruit; ie, they pH-balance the dish.

It is important to recognize that these ideas and their practical applications in clinical practice have evolved over a period of many years. By reporting a series of worst-case, PPI-resistant patients who had successful outcomes with a strict low-acid diet, it is my hope to stimulate interdisciplinary research in the areas of reflux, nutrition, and the American diet. Indeed, the contemporary American diet appears to be making Americans sick.

SCIENTIFIC BASIS FOR DIETARY ACID RESTRICTION IN REFLUX MANAGEMENT

Despite the popular use of the term “acid reflux” among the lay public, most of the clinical manifestations of LPR and GERD are due to pepsin.^{1,3,5,7-9,11-17} Pepsin is responsible for tissue injury and inflammation, and the confusion stems from the fact that pepsin requires acid activation.^{1,14} The pepsin activity profile (see Figure), the cell biology of LPR, and clinical experience with pharyngeal pH monitoring all suggest that the threshold of the larynx for peptic injury is far less than that of the esophagus.^{1,8,11-17} Surprisingly little acid is needed for peptic activation, and pepsin remains mildly proteolytic up to pH 6.5.¹⁴ In addition, tissue-bound pepsin can be acti-

vated by hydrogen ions from any (including a dietary) source.¹⁴

It appears that the key to the development of clinical laryngeal disease is the presence of tissue-bound pepsin,^{8,9} which causes depletion of protective cell proteins such as carbonic anhydrase, E-cadherin, and the stress (“heat-shock”) proteins.^{8,9,12,13} Johnston et al⁸ demonstrated (in vitro and in vivo) that peptic laryngeal damage occurs at pH 5. It was basic science that led us to consider the possibility that the contemporary reflux epidemic might be related to the contemporary American diet.

INCREASING PREVALENCE OF REFLUX DISEASE AND REFLUX-RELATED ESOPHAGEAL CANCER

The prevalence of acid reflux disease (GERD and LPR) has increased dramatically in our lifetimes.^{24,25} Using a Poisson model and an analysis of 17 prevalence studies, El-Serag²⁴ showed that since 1976, the mean rate of increase of GERD has been a staggering 4% per year ($p < 0.0001$).

Altman et al²⁵ reported that office visits to otolaryngologists for LPR increased almost 500% from 1990 to 2001. Those authors hypothesized that the increase was due to obesity and a greater awareness of LPR by otolaryngologists²⁵; however, reportedly, only 27% of the study patients were counseled about an antireflux diet.²⁵

An even more ominous trend is the skyrocketing increase in the prevalence of esophageal cancer in the United States.²⁶⁻³⁰ The US National Cancer Institute data from 2005 reveal that esophageal cancer had increased 600% since 1975 (from 4 to 23 cases per million).²⁶ During this same period, its mortality rate increased sevenfold, despite increased esophageal surveillance^{26,27}; the histopathology has been trending toward more deadly, poorly differentiated adenocarcinomas.^{27,28}

In addition, the prevalence of Barrett’s esophagus (a reflux-related precursor to esophageal cancer) is also very high.²⁷⁻³⁰ Reavis et al²⁹ reported that patients with hoarseness, sore throat, and chronic cough (LPR symptoms) had Barrett’s esophagus just as frequently (7% to 10%) as did patients with GERD and heartburn. Thus, routine esophageal screening for both LPR and GERD was (and still is) recommended.^{29,30}

INCREASED PREVALENCE OF REFLUX IN YOUNG PATIENTS

In 2010, we estimated the prevalence of reflux (GERD and LPR) in the United States by interviewing 656 adult US citizens while they were waiting in line to purchase discount theater tickets in Times Square in New York City. (This specific location

appeared to provide us with a reasonable approximation of a national sample.) The interviews were carefully conducted to elicit all reflux symptoms and medications, both over-the-counter and physician-prescribed. Respondents were considered to have a tendency to reflux if they had multiple reflux symptoms and/or took reflux medications. For the purposes of this survey, respondents with only one symptom, such as hoarseness or cough, were not considered to have reflux, as one symptom may have many different causes.

The data revealed that an astonishing 40% (262 of 656) of the study group had reflux disease, with 22% (144 of 656) having classic GERD and another 18% (118 of 656) having LPR. There were no statistical differences between age groups, genders, and regions of the country. The most striking and unanticipated result was that 37% of the 21- to 30-year-old age group had reflux.

In the past, reflux was primarily a disease of overweight, middle-aged people. Now, we are finding that many of our reflux patients are neither old nor obese.¹⁰ This trend toward younger and younger patients with more and more severe reflux has been noted by other experienced clinicians (J. Hunter and R. Sataloff, personal communications, 2011).

CHANGES IN AMERICAN DIET IN PAST FIFTY YEARS

Coincident with the reflux epidemic, the American diet has changed dramatically.³¹⁻³⁶ Since the 1960s, there have been four parallel unhealthy dietary trends: 1) increased saturated fat; 2) increased high-fructose corn syrup; 3) increased exposure to organic pollutants (eg, DDT, PCBs, dioxins); and 4) increased acidity.³³⁻³⁵ The last of these trends — increased dietary acid — may hold the key to understanding the contemporary reflux epidemic and the dramatic increases in Barrett’s esophagus and esophageal cancer.^{29,33,34}

In 1973, after an outbreak of food poisoning (botulism), the US Congress enacted Title 21, mandating that the US Food and Drug Administration (FDA) ensure the safety of processed food crossing state lines by establishing “Good Manufacturing Practices.”^{33,34} How was this accomplished? Through acidification of bottled and canned foods, which was intended to prevent bacterial growth and prolong shelf life. For two generations, the FDA has never wavered from this path, apparently without ever considering the possibility that the acidification of America’s food supply might have potential adverse health consequences. From the 1979 Title 21 Act³⁴:

Acidified foods should be so manufactured, processed, and packaged that a finished equilibrium pH value of 4.6

or lower is achieved. If the finished equilibrium pH is 4.0 or below, then the measurement of acidity of the final product may be made by any suitable method. [April 1, 2002; US Government Printing Office, 21CFR114.80]

In other words, the FDA actually encourages food manufacturers to reduce the pH of their products to less than 4.0, the same pH level as stomach acid.¹ In addition to acetic, ascorbic, citric, and hydrochloric acids as food additives, the FDA allows more than 300 other chemicals that are “generally regarded as safe” (GRAS).³³⁻³⁶ Many of these GRAS food additives were approved in the 1970s without the benefit of contemporary methods of scientific testing and analysis.^{34,36}

Furthermore, in 1997, the FDA was directed to provide specific criteria for food manufacturers to report their use of GRAS additives in their products; inexplicably, as of this writing, those criteria have still not been established.³⁶ Thus, with regard to food additives, the food industry remains completely self-regulated.^{33,36}

In 2010, the US Government Accountability Office, a bipartisan group of scientists, published a scathing report on the FDA’s lack of oversight of food manufacturing.³⁶ In particular, they were critical of the FDA’s negligence in failing to monitor GRAS food additives, as referenced above.³³⁻³⁵ In searching the literature, it appears that neither the FDA nor the scientific community have examined the acidity question. No one, it appears, has considered the possibility that the acidification of the nation’s food might have potentially adverse health consequences; today, almost all food that is bottled or canned is below pH 4.³³

It is interesting to note that the Amish, who grow and consume their own organic food, have aerodigestive tract cancer rates (eg, larynx, pharynx, esophagus) that are only 37% the rates of controls.³⁷ In attempting to explain those findings, the authors emphasized that the Amish do not drink alcohol or smoke tobacco, but they did not discuss or consider the possible health benefits of a diet devoid of acids and other food additives.³⁷

DIETARY ACID AS POSSIBLE MISSING LINK IN REFLUX EPIDEMIC

Why are reflux disease and esophageal cancer epidemic? Many years ago, when esophageal can-

cer was relatively uncommon, reflux patients usually presented in middle age. Today, we are seeing comparable disease in patients in their twenties (J. Hunter and R. Sataloff, personal communications, 2011). Overacidity in the diet may be the missing link that explains the reflux epidemic, as well as increasing rates of Barrett’s esophagus and esophageal cancer.

At present, even baby food is acidified. We tested the acidity of an “organic” banana baby food and found it to be pH 4.3; normally, banana is pH 5.7. The label of the so-called “organic” banana product revealed that it had had both ascorbic and citric acids added. Indeed, almost all bottled and canned foods and beverages contain ascorbic acid and/or citric acid; sometimes the packaging is less obvious and may just read “vitamin C-enriched” or “vitamin C-enhanced.”³³

Knowing what we now know about the cell biology of reflux, the stability and activity of pepsin, and the contemporary American diet, it is reasonable to postulate that the acidification of America’s food supply may be responsible for the reflux epidemic. Diet may be the primary factor in the prevalence, mechanisms, manifestations (including neoplasia), and outcomes of reflux disease, particularly as it affects the laryngopharynx and esophagus. Further research is needed to investigate this question. Until now, it appears that fundamental nutritional issues related to how food has been preserved for the past two generations may have been overlooked. Dietary acid may turn out to have serious adverse health effects on the general population, and how food is preserved may soon become a perplexing public health conundrum. In the meanwhile, it seems likely that patients with LPR will benefit from a low-acid diet.

CONCLUSIONS

A strict low-acid (“acid-free”) diet appears to be beneficial for patients with pH-documented LPR. In this study, the diet was shown to improve both the symptoms and the laryngeal findings of patients with recalcitrant (PPI-resistant) LPR. Also raised by this study are broader public health policy issues related to FDA-mandated acidification of manufactured foods and beverages.

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