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Management of upper gastrointestinal symptoms in patients with autoimmune gastritis

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Abstract

Purpose of review: Autoimmune gastritis is characterized by atrophy of acid secreting parietal cells resulting in achlorhydria. Upper gastrointestinal symptoms are common in autoimmune gastritis and frequently result in prescriptions for acid suppressant medications despite the inability of the stomach to secrete acid. Evidence-based recommendations for management of gastrointestinal symptoms in autoimmune gastritis are lacking.

Recent findings: The most common symptoms in patients with autoimmune gastritis are dyspepsia, heartburn, and regurgitation. Gastroesophageal reflux should be confirmed by pH-impedance testing and is typically weakly acid or alkaline. Therapy for reflux focuses on mechanical prevention of reflux (i.e., elevation of the head of the bed and alginates) or when severe, anti-reflux surgery. The etiology of dyspepsia in autoimmune gastritis is unclear and largely unstudied. In the first half of the 20th century, oral administration of acid to “aid digestion” was widely used with reported success. However, randomized, placebo-controlled trials are lacking. Here, we provide suggestions for attempting gastric acidification therapy.

Summary: Upper GI symptoms are common in autoimmune gastritis. Their pathogenesis and therapy remain incompletely understood. Acid suppressant medications are useless and should be discontinued. A trial of acid replacement therapy is recommended especially in the form of placebo-controlled trials.

Keywords

Autoimmune gastritis; dyspepsia; gastroesophageal reflux; achlorhydria; acid therapy

Introduction

Autoimmune gastritis (AIG) is an organ-specific immune-mediated condition characterized by atrophy of acid secreting parietal cells which results in hypo- or achlorhydria.

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Compensatory hypergastrinemia can result in hyperplasia of enterochromaffin-like cells (ECL) and the development of gastric neuroendocrine (carcinoid) tumors [1*–5]. The prevalence of AIG in the general population of the United States (US) is approximately 1% with a 2:1 female predominance [6]. AIG is often accompanied by other autoimmune diseases such as Hashimoto thyroiditis (36-60%) [7,8], Graves' disease [9], type 1 diabetes (6-10%) [10], celiac disease, vitiligo, and primary biliary cholangitis [11]. The classic hematological manifestation of AIG is vitamin B12 (pernicious) anemia due to the lack of intrinsic factor. However, as achlorhydria may antedate pernicious anemia by as long as 35 years, B12 deficiency is typically a late finding in AIG patients [12]. Iron deficiency is the most frequent hematological manifestation [13] and the prevalence of iron and B12 deficiency in AIG patients are estimated to be 50% and 37-60% respectively [14]. AIG-induced achlorhydria also increases risk of small intestinal bacterial overgrowth and enteric infections [15*].

Both *Helicobacter pylori* gastritis and AIG are associated with parietal cell and intrinsic factor antibodies and vitamin B12 deficiency [15*–17]. AIG is distinguished from *H. pylori*-associated corpus-predominant atrophic gastritis by histology as only AIG has normal or near normal antral mucosa [2,18*]. Until recently, AIG was thought to be a precursor to gastric adenocarcinoma. However, this is now considered a spurious correlation arising from the frequent co-existence of the two diseases in the past [3,19]. Nonetheless, AIG is associate with an increased the risk of type I gastric neuroendocrine tumors arising in response to the sustained hypergastrinemia caused by the loss of feedback acid inhibition of gastrin release which has a trophic effect on ECL cells. Type I gastric neuroendocrine tumors occur in 0.4 to 0.7% of AIG patients per year [20,21]; this risk is responsible for the recommendation for endoscopic surveillance at 3-to-5-year intervals [16*,22]. Although the "textbook" association of AIG is with pernicious anemia, clinically most patients come to medical attention because of infertility or gastrointestinal symptoms [2,23,24]. In fact, many patients are receiving antacids or antisecretory drugs when first diagnosed [25]. This review focuses on clinical management of upper gastrointestinal (GI) complaints in patients with AIG.

Gastrointestinal symptoms in patients with AIG

The prevalence of GI symptoms in AIG is reflected in a retrospective analysis of 379 AIG patients who were screened using the Rome III criteria. GI symptoms were reported in 57% of this cohort; in which 69.8% reported upper GI symptoms exclusively with dyspepsia, subtype postprandial distress syndrome being most frequent (60%). Coexisting lower GI symptoms were present in 14.4% with 15.8% having exclusively lower GI symptoms [23]. Another study of 99 patients confirmed the high prevalence of epigastric pain (35%), heartburn (24%), nausea (22%) and bloating (17%), in comparison with lower GI symptoms: diarrhea (15%) and constipation (4%) [2]. Carabotti et al. evaluated 54 consecutive AIG patients and reported typical GERD symptoms in 24% with 9.2% of patients complaining of heartburn and 18.5% of regurgitation [26]. The most common conditions prompting investigation in patients who were subsequently diagnosed with AIG were abdominal bloating-related symptoms (47%) and iron/vitamin B12 deficiency anemia in 33% [27].

The average time between the symptomatic presentation to AIG diagnosis was 14 months [28].

In the past, dyspeptic symptoms in patients with reduced acid secretion were usually attributed to impaired digestion caused by lack of acid and pepsin and a delay in gastric emptying [29,30]. The delay in emptying of primarily solids has been considered related to reduced volume and acidity of secretions causing slow liquification of the protein in meals (i.e., related to the absence of acid and pepsin rather than an intrinsic abnormality in gastric motility). Recent studies have confirmed delayed gastric emptying of protein-containing meals but not with inert objects in AIG. This delay can also be shown with antisecretory drug therapy. As might be expected, the degree of delay correlates with higher gastrin levels and the degree of atrophy [31].

Normally, acid entering the duodenum results in forward movement of duodenal contents which also reduces regurgitation of duodenal contents into the stomach [32]. The lack of acid secretions reduces this forward motion and increases the likelihood of duodenogastric reflux which theoretically would increase the exposure of the gastric mucosa to bile [32]. The bile present in the stomach consists largely of taurine conjugated bile acids as glycine-conjugated bile acids in the stomach are normally precipitated by the acid pH of the stomach. Achlorhydria and bacterial overgrowth would likely increase the concentration of unconjugated bile acids which are more injurious to the gastric and esophageal mucosa than their conjugated counterparts [33]. However, with one exception noted below there is little evidence for a significant role of bile acids in AIG-associated dyspepsia or a response to bile acid sequestrants [34]. Other potential culprits causing dyspepsia include the products produced by the large and varied bacterial or fungal populations in the achlorhydric stomach such as lactic acid from *Lactobacilli* [35*].

GERD symptoms are common in AIG. The first series of patients with achlorhydria and erosive esophagitis was published by Palmer in 1960 and, although many AIG papers quote that reference, it is important to note that only 1 patient had pernicious anemia and 18 of 22 had gastric resection surgery [36]. In 1973, Orlando and Bozymski reported studies on a patient with AIG experiencing heartburn and regurgitation of bilious material [34]. This patient had a small hiatal hernia, a manometrically incompetent lower esophageal sphincter and a radiologic water test confirming gastroesophageal reflux. In addition, pyloric sphincter manometry and duodenal perfusion with saline and 0.1N HCl confirmed an incompetent pylori sphincter (i.e., duodenal acidification failed to reduce duodenal gastric reflux and the amount of reflux through the pyloric sphincter was not deceased by duodenal acidification) [34,37]. Bile acid perfusion of the esophagus elicited burning retrosternal pain and symptom relief was obtained by with the bile acid binding resin cholestyramine. Importantly, the authors note that prior studies of AIG patients did not report abnormal pyloric sphincter function. This suggests that their patient was a unique subject with incompetence of both the lower esophageal and pyloric sphincters [34].

More recently, with the advent of impedance-pH monitoring, GERD symptoms in AIG have been associated weakly acidic and alkaline reflux [25,38,39]. For instance, 10 of 41 AIG patients undergoing impedance-pH monitoring had positive tests for GERD but only 1

patient had abnormal acid exposure pH <4.038. In that study, there were no differences in the median gastric pH (6.0 vs 6.3, p=0.959) and total number of reflux and non-acid reflux episodes between symptomatic and asymptomatic patients. Two patients with dyspepsia showed a positive correlation between epigastric pain and non-acid reflux. Interestingly, 61% of symptomatic patients were receiving acid suppressant medications despite a mean basal gastric pH of 6.3 [38].

Endoscopic evidence of GERD (erosive esophagitis or Barrett's esophagus) in AIG is rare. Indeed, in a cohort of 54 AIG patients, only 2 (3.7%) had LA grade C esophagitis and C2M2 Barrett's esophagus per Prague classification [26]. There are also rare reports of patients with very short segments of Barrett's esophagus and AIG (C0M1) [40]. As AIG typically occurs late in life and Barrett's, once present, tends to remain, it seems likely Barrett's esophagus preceded the onset of AIG. Studies of *H. pylori*-induced gastric atrophy have shown an inverse association of gastric atrophy and Barret's esophagus (OR 0.34 [0.10-1.24]) [41].

Potential role of the gastric microbiome

Achlorhydria results in alterations in the gastric microbiota. The achlorhydric stomach has been described as a petri dish [1*]. The gastric microbiome has been of interest since the discovery of bacteria by Pasteur and Koch [35*]. The average stomach in adults in the 19th and early 20th century had reduced acid secretion and high populations of cultivable bacteria [42]. The high levels of *Lactobacilli* (called the Boas-Oppler bacillus) in the stomach were considered indicative of the presence gastric cancer [43,44]. Studies of cultivable bacteria in the stomach of patients with achlorhydria, gastric cancer, or peptic ulcers have reported that the microbial diversity and density increases along with the mean gastric pH [45–50] with the total number of organisms/mL ranging from 5.6 to 9.2 organisms, log10/mL [46]. Modern studies using molecular techniques have confirmed that AIG stomachs exhibit a relatively high microbial diversity in comparison to *H. pylori*-induced atrophy [51]. These bacterial and fungal populations have the potential to produce a large variety of chemical products that may alter gastric function and cause symptoms.

Pharmacologic management of symptoms in AIG

Gastroenterologists are usually not the first healthcare providers to see the patient with AIG. Many patients are already taking an acid suppressant medication, and these should be discontinued as their physiologic targets are absent. Evaluation of symptoms should start with upper endoscopy and includes gastric antral and body biopsies, placed in separate containers; this serves the dual purpose of surveillance for tumors, examination of the distal esophagus, gastric and duodenal mucosa, and histologic confirmation of atrophic gastritis. Esophageal pH study with impedance should be done to confirm non-acid GERD and explore if there is a positive symptom correlation between symptoms and non-acid reflux.

Older research of dyspepsia in AIG focused on acid replacement therapy with and without pepsin. The primary outcome sought was improvement or relief of abdominal pain. Interpretation is complicated by the fact that these studies were done in the era before

the introduction of double-blind placebo-controlled trials or serious consideration of the placebo effect. Although patients with AIG can present with delayed gastric emptying, this is considered physiologic and studies to explore a possible benefit with prokinetic treatment are lacking.

As noted above, weakly acidic and alkaline reflux is associated with GERD symptoms in AIG patients [25,38,39]. The therapeutic options for GERD in AIG include lifestyle modification such as elevation of head of the bed and avoiding late meals. The pharmacological options of non-acid GERD in the literature have been mostly extrapolated from bile acid gastropathy. These include antacid/alginate combinations, prokinetics, ursodeoxycholic acid and bile acid sequestrants [52,53]. Importantly, Nissen fundoplication was a successful treatment for one confirmed non-acid reflux AIG patient suggesting a possible role for endoscopic or surgical anti-reflux therapy [54].

Hydrochloric acid (HCl) replacement therapy

By the 1870s, dyspepsia and other GI symptoms were thought to be related to the absence of gastric acid [55,56] and HCl was administered to aid digestion, stimulate pepsin release, regulate intestinal motility and as an antiseptic [57,58]. In 1934 Hurst wrote “until recently, it was assumed that the discovery of achlorhydria was an indication for treatment with hydrochloric acid” [30]. He recommended prescribing gastric acid replacement with 1 to 2 drachms (~4 to 8 mL) of dilute HCl in 8 to 10 ounces of water, three times daily before meals [30]. HCl was generally given to tolerance and ranged from 10 to 90 drops given three times daily (Table 1) [59]. One goal of acid therapy was to activate pepsin but by 1913, it was known that oral HCl was ineffective in appreciably modifying protein digestion in patients with achlorhydria [60]. In the normal stomach, the HCl introduced is rapidly emptied or neutralized by the meal [61]. A 1942 study of 300 patients with achlorhydria treated with HCl reported improvement of GI symptoms in 76% [62]. It is important to reemphasize that placebo-controlled studies of HCl and HCl with pepsin are not available.

HCl substitutes

The use of liquid HCl is inconvenient and has largely been superseded by use of solid dosage forms of amino acid hydrochlorides that dissociate in the stomach to the amino acid and HCl. Examples are glutamic acid hydrochloride and the HCl salt of betaine (Betaine HCl) [58,63]. Betaine hydrochloride should not be confused with trimethylglycine (TMG), which does not produce HCl. Although Betaine HCl was banned by the US Food and drug administration (FDA) in 1993 for use as a gastric acid supplement because of insufficient evidence to classify it as “generally recognized as safe and effective,” (US Code of Federal Regulations, Title 21, Section 310.540) it remains readily available in health food markets with or without a fixed dosage of pepsin [64,65]. The typical dosage for reducing gastric pH is two 750 mg Betaine HCl tablets, which in normal volunteers with proton pump inhibitor-induced hypochlorhydria (i.e., pH >4) maintained the intragastric pH below 3 for less than 75 minutes when taken fasting [66,67]. When taken just before a small meal (336 kcal), the duration of effect is decreased. Overall, pharmacological studies aiming to improve the absorption of medications have shown Betaine HCl to be well tolerated and

effective at reducing gastric pH [67]. An observational study of 70 patients who met Rome III criteria for functional dyspepsia, reported that a combination of amino acid hydrochloride and pepsin achieved a >50% symptom improvement in 30.8% of the patients after 6 weeks [63]. Controlled placebo-controlled studies are lacking.

Other agents utilized for gastric acidification to a pH between 2-3 include Coca-Cola [67] and organic acids [68] (Table 1). Citric acid or malic acid are available in both in capsule and in bulk in grocery stores or online at a low cost (8-16 cents/g and 6-15 cents/g respectively). One recommendation for administration of citric acid is 150 to 300 mg diluted in 500 ml of water divided in 2 doses [69]. Citric acid is used in the urea breath test typically in doses up to 4 grams in about 8 oz of water (Table 1). Apple cider vinegar which contains acetic acid is currently very popular and widely available in grocery stores (e.g., Bragg Apple Cider Vinegar containing 5% acetic acid) and the recommended dose is 15 to 30 ml/day in 8 oz of water in 2 doses [70]. Importantly, the effect of the administration of acids either after or with food is short as the acid is rapidly consumed by its interaction with dietary protein; the rapidity of the loss is proportional to the buffering capacity of the meal [58,71]. Because of the reduction or absence of normal acid secretion, the volume of the gastric contents tends to be decreased and one should increase daily fluid intake with meals to at least 2 glasses (16 oz)/meal. Experiments as to the optimum dosages are lacking and likely is individual-specific. We suggest that one start with low doses and if a good response is lacking, increase to tolerance. Patients will need to experiment what works best regarding dosage and timing of administration (e.g., before, during or after meals). All acid drinks may theoretically damage tooth enamel [72] and all are tart. Use of a straw is suggested to reduce exposure to the tooth enamel and the addition of aspartame or honey can reduce tartness.

Antiacids, Sucralfate, and antisecretory agents

Alginate therapy (e.g., Gaviscon) has been used successfully in Europe to treat GERD symptoms in AIG patients. It is important to note that the Gaviscon formula varies from country to country; the crucial difference is the concentration of alginate. For example, the Gaviscon Advance® version available in the U.K. contains 1000 mg of sodium alginate, meanwhile, the U.S. version contains only 250 mg of sodium alginate [73]. Alginates have been effective in the treatment of heartburn, regurgitation, and dyspepsia in patients with general GERD symptoms, before differentiation of non-acid vs. acid reflux on pH impedance studies [74,75]. Conversely, sucralfate has not been studied in AIG patients. Six grams/day did not produce symptom improvement in bile gastritis [76]. As noted above, the lack of functioning parietal cells in AIG assures the futility of anti-secretory therapy.

Conclusion

Digestive complains are common in patients with AIG. Most common are dyspepsia and GERD symptoms. Evaluation of upper GI tract symptoms in AIG should include upper gastrointestinal endoscopy and esophageal combined impedance-pH studies (Figure 1). Therapy for weakly acid or non-acid GERD primarily consists of use of mechanical barriers to prevent reflux (elevation of the head of the bed, avoidance of late-night meals, etc.) and alginates. Acid suppressant medications should be discontinued as their physiology targets

are absent. For resistant symptoms in patients with confirmed reflux, endoscopic or surgical fundoplication should be considered. The pathogenesis of post prandial dyspepsia in AIG patients is unclear. Historically, administration of HCl has been used successfully. There are few recent studies and no adequately controlled trials to confirm that the benefits are not placebo effects. For dyspepsia, we recommend increasing the volume of fluid taken with the meal and a trial of traditional acid replacement therapy. There are a variety of options to temporally acidify the stomach to a pH between 2 and 3.5 including acidic drinks (lemon juice, Coca Cola®, etc) given with and/or after meals. Other options are HCl diluted in water, Betaine HCl tablets or mixing organic acids in water (Table 1). The solid dosage form of the organic acids (citric, malic, and tartaric acids) weigh approximately 5 gm/teaspoon. Symptomatic AIG remains as a therapeutic frontier as detailed clinical descriptions of the associated dyspepsia and placebo-controlled trials are both lacking and sorely needed.

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Potential conflicts:

Dr. Graham is a consultant for RedHill Biopharma and Phathom Pharmaceuticals regarding novel *H. pylori* therapies and has received research support for culture of *Helicobacter pylori*. He is also a consultant for DiaSorin regarding *H. pylori* diagnostics and with Otsuka Japan regarding novel breath tests. He has ongoing collaborative research projects with American Molecular regarding molecular diagnostics for *H. pylori*. He was the PI of an international study of the use of antimycobacterial therapy for Crohn's disease. Dr. Gomez Cifuentes has nothing to declare. Dr. Sparkman has nothing to declare.

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Key points

1. The most common symptoms in AIG are dyspepsia and typical gastroesophageal reflux (GERD) symptoms.
2. Typical GERD symptoms are caused by weakly acid and alkaline reflux, the exact mechanism behind dyspepsia is unknown.
3. Acid suppressant medications should be discontinued as their physiologic targets are absent in AIG patients.
4. Therapy for AIG patients should be approached based on the predominant symptoms of GERD and dyspepsia.

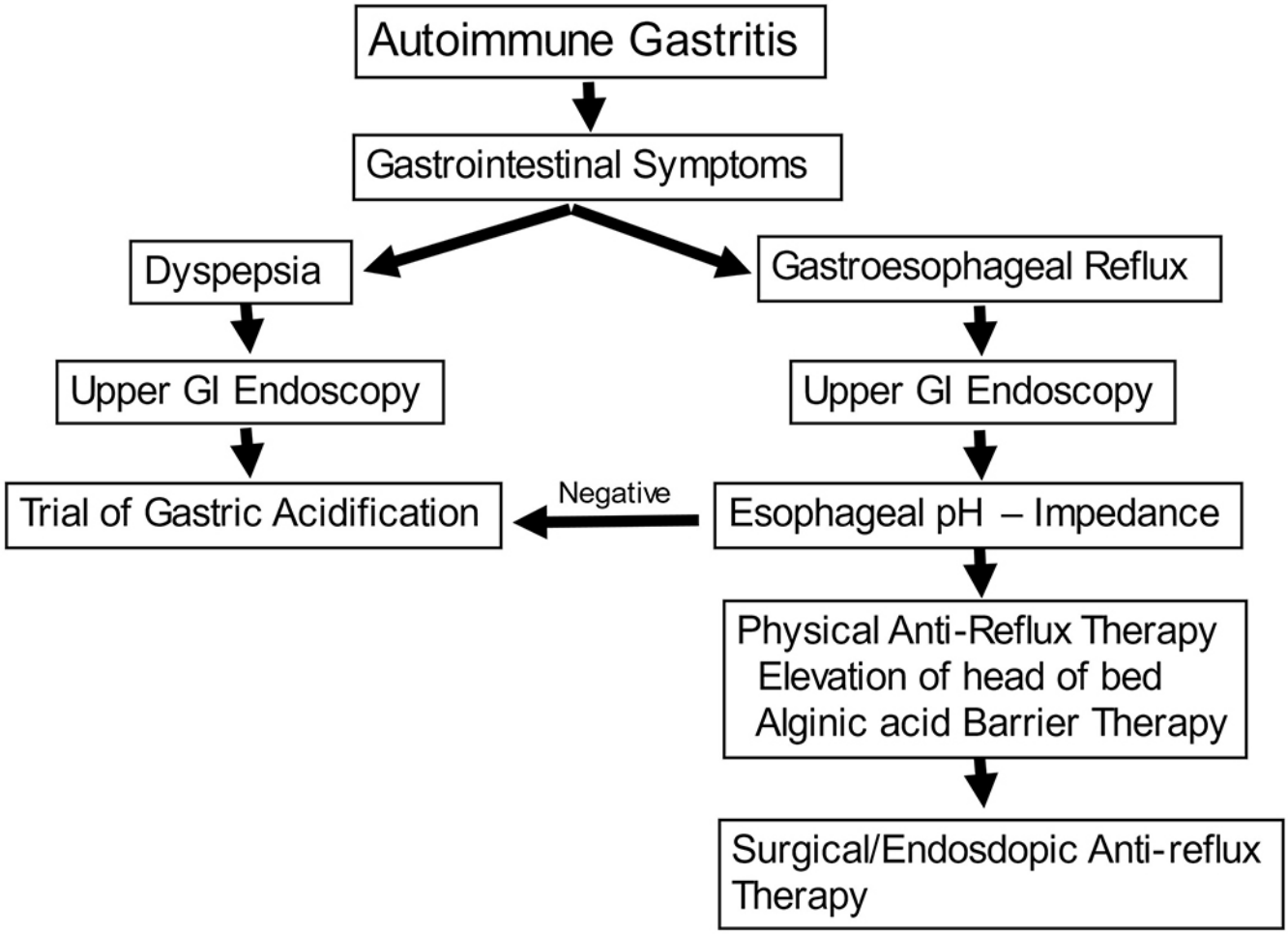

Figure:
Algorithm for the diagnosis and treatment of upper gastrointestinal symptoms in patients with autoimmune gastritis.

Table 1.

Approximate pH of acids added to 240 mL (8 oz) of water.

Acid Source	Amount/ 240 mL H_2O	Teaspoon/ 240 mL H_2O	pH range
Citric or Malic acids	1.25 to 4 gm	¼ to ¾	2.07 to 2.43
	mL/240 mL H_2O	**Tablespoons/240 mL H_2O**	**pH range**
Acetic acid	7.5 to 30 mL	½ to 2	2.21 to 2.50
	Drops/240 mL H_2O	**mL/240 mL H_2O**	**pH range**
HCl 10%	1 to 80 gtt	0.05 to 4 mL	1.26 to 3.20

Recommended doses are from 1 to 4 grams/dose [e.g., ¼ teaspoon to ¾ tablespoon in 240 mL (8 oz) water]. Higher doses are tart and tolerability can often be improved with the addition of an artificial sweetener or honey. Most vinegars are 5 to 6% acetic acid liquid with the usual dose being 15 to 30 mL (1 to 2 tablespoons) in 240 mL (8 oz) water. We recommend starting with low doses given with meals and increase as needed up to the maximum dosage.