



Lactose Intolerance and Milk Protein Allergy

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Abstract

Purpose of review Real or perceived lactose intolerance (LI) and true cow's milk allergy (CMA) are common reasons for dairy avoidance but are underdiagnosed and under-treated. Dairy avoidance is associated with nutrient deficiencies and unintended health consequences that disproportionately affect minorities.

Recent findings Surveyed GI physicians report that at least 30% of their patients had LI and 16% had food allergies including CMA. In a 2019 survey, approximately 10.8% of adults have symptoms consistent with a food allergy and CMA was the second most common allergy reported. LI and CMA are more common in ethnic and racial minorities and occur more often in women. Treatment options are poorly implemented, in part, due to decreased awareness of the current guidelines.

Summary Dairy food consumption reduces risk for chronic disease states and remains first-line intervention for LI. Dairy avoidance and nutrient supplementation are effective in managing CMA. Methods to guide dairy food reintroduction, improve LI education, with ethnic and racial considerations and facilitate early identification of CMA are needed. The optimal nutrient supplementation strategy remains undefined.

Introduction

Real or perceived lactose intolerance (LI) and cow's milk protein allergy (CMA) remain common reasons for dairy avoidance [1••]. Dairy avoidance is associated with unintended health consequences including diabetes, hypertension, cardiovascular disease, obesity, and

diet-related malignancies such as colon cancer. Without supplementation, diet quality is impaired, and nutrient deficiencies occur [2]. LI is a clinical syndrome due to symptomatic digestion of lactose, but dairy avoidance is not required [3]. Because CMA is an allergic reaction to

the milk protein with the potential risk of anaphylaxis [4], one must correctly identify CMA early and distinguish it from LI as dairy avoidance is indicated and supplementation required (see Table 1). Nutrient supplementation is an effective intervention in managing

patients who avoid or limit dairy foods to prevent clinical and subclinical nutritional deficiencies [5]. This review will discuss current management strategies for lactose intolerance and highlight emerging treatment options for the management of CMA.

Lactose intolerance

Clinicians treating lactose intolerant patients are encouraged to review the 2010 National Institutes of Health Lactose Intolerance Consensus Statement [6••]. Key findings by the expert panel include the determination that “lactose intolerance is a real and important clinical syndrome, but its true prevalence is not known” because of differing definitions in the literature. Real or perceived LI increases the risk of consuming a nutrient deficient diet which is associated with an increased incidence of hypertension, diabetes, and cardiovascular disease including stroke and diet-related malignancies such as colon cancer, which are more common in minority populations. The panel identified that LI is more common in ethnic minorities but less common than previously reported. Perceptions of dairy tolerance and understanding of the clinical benefit impacted the success of treatment plans, particularly in racially and ethnically diverse populations. Therefore, LI education programs should include an explanation of the relationship of diet nutrient content to chronic disease risk reduction and explain the health benefits, especially for minority patients. The main goals of treating a LI individual with dairy foods are to prevent the

Table 1. Lactose intolerance versus Cow's Milk Protein Allergy. Ref: [1••, 6••, 10]

	Lactose Intolerance	Cow's Milk Protein Allergy
Cause of symptoms	Lactose (poor digestion)	Milk Protein (allergic reaction)
Age of onset	Rare before age 2 years	Any age; childhood onset at age 1 year; often outgrown by 3 years of age
Site of reaction	GI tract (Intraluminal)	Immune system
Systems involved in the reaction	GI tract only	GI tract, skin and respiratory systems
Onset of symptoms	Several hours post ingestion	Less than 1-2 hours post ingestion
Common Symptoms	Nausea, vomiting, gas, bloat diarrhea, abdominal pain, borborygmi, abdominal cramps	Rash, eczema, hives, edema, headache, wheezing shortness of breath, anaphylaxis
Diagnostic confirmation	Lactose breath hydrogen test	Skin prick test, Allergy testing
Dairy food consumption	Yes; some require dietary modification ± lactase replacement	No; Use alternatives beverages and supplement nutrient deficiencies
Affected children	Female > Male	Male > Female
Affected adults	Female > Male	Female > Male

nutrient shortfalls and the unintended health consequences associated with dairy food avoidance. The report encouraged objective testing prior to treatment, patient education about LI, research to improve implementation strategies, behavior modification, and the need to identify the optimal supplementation when dairy avoidance is needed.

Lactose digestion occurs in the proximal small bowel where the milk sugar, lactose, is digested by the enzyme, lactase, found on small intestinal microvilli. Lactose maldigestion (LM) is the intraluminal process that occurs when there is hypolactasia (i.e., low enzyme levels) causing incomplete digestion of lactose in the small bowel leading to colonic bacteria digesting the lactose but is asymptomatic in most adults. The activity level of the bacterial lactase enzyme is regulated by the amount of lactose present in the colon and varies by species of the intestinal flora. Primary hypolactasia is the normal age-related decline in lactase activity. Secondary hypolactasia occurs when there is damage to the intestinal villi resulting in a temporary loss or reduction of the lactase levels until mucosal healing occurs. One only needs 50% lactase activity for normal digestion of dairy foods. Understanding this pathophysiology helps patients to understand and comply with the treatment strategies for LI [7].

To determine if the 2010 Expert Panel recommendations [6••] were influencing clinical practice, 298 members of the American Gastroenterological Association were surveyed in 2013 to identify their management strategies for patients with LI and food allergies [8]. Most physicians surveyed (97%) reported that at least 30% of their patients were LI and 16% had food allergies including CMA. Their affected patients were more likely to be female (59%), ages 18–49 years (38%) and minority (24% African American, 14% Hispanic, and 11% Asian). While acknowledging that 64% of their patients sought solutions that included dairy foods in the diet, the majority (70%) of the healthcare providers recommended dairy avoidance. Despite risk for nutrient deficiencies, only 50% the physician respondents recommended vitamin or nutrient supplementation. Of those that suggested dietary modification that included dairy foods, only 47% of the recommendations met the goals of the 2010 dietary guidelines.

Other clinical conditions may also present with a similar clinical presentation, so it is helpful to remember that “All that rumbles is not lactose intolerance” [9]. The GI symptoms associated with symptomatic LM include diarrhea, abdominal bloating, distension, excessive flatus, borborygmi, and eructations. The most common mimickers of lactose intolerance are listed in Table 2. LI must be distinguished from a CMA before treating LI [10, 11]. In addition, there are short-chain soluble oligosaccharides and long-chain fermentable fibers, which

Table 2. Mimickers of Lactose Intolerance

Mimickers of Lactose Intolerance		
milk protein allergy	Celiac disease	SIBO
Irritable bowel syndrome	Inflammatory bowel disease	GERD
Fructose intolerance	Microscopic colitis	

SIBO: small intestinal bacterial overgrowth; GERD: gastroesophageal reflux disease; Ref: [10, 11]

can produce non-specific GI symptoms. Patients with IBS are particularly prone to the different GI effects (i.e., gas, bloating, distension, and flatulence) of dietary fiber despite the health benefits of fiber in the treatment of IBS. Even in healthy individuals, dietary fiber may cause the same non-specific symptoms as LI [12].

The lactose breath hydrogen test remains an imperfect gold standard to confirm LI, although the optimal dose of lactose is debated [13, 14]. It identifies intraluminal LM by colonic bacteria based on the peak rise of expelled breath measured at 30-min intervals for 3 h (or 20-min intervals for 2 h in bariatric patients) [15, 16]. The test is limited by the duration of testing and lack of direct correlation with clinical symptoms. The patient must also be able to blow up a balloon which negatively impacts the very young, the disabled, acutely ill patients, those with lung health issues and some elderly patients. Yet, it remains the best tool that clinically available and it has been standardized in multiple clinical trials.

The term, LI, is reserved for the clinical syndrome that occurs when the intraluminal process, LM, causes reproducibly and temporally associated clinical symptoms following the ingestion of lactose. The presence of both components is required to meet diagnostic criteria [6••]. The current approaches to LI are three-fold: dairy avoidance, strategies to minimize symptoms, and interventions that improve digestion. The importance of working with a registered dietitian is underscored as they are skilled in diet counseling and nutritional management.

Dairy avoidance is often recommended by well-intentioned but uninformed healthcare providers or self-selected by the symptomatic patient but is not a recommended solution. The most common nutrient deficiencies associated with a dairy-free diet include calcium, vitamin D, magnesium, phosphorus, riboflavin, vitamin A, and protein. These micronutrient deficiencies increase the risk for chronic diseases states as noted above [1••, 6••]. Cifelli et al. found that even when plant-based nutrients were increased, the nutrient deficiencies associated with dairy avoidance were not reversed. These deficiencies are reversed when dairy foods are added to the diet [17, 18]. Nickalas et al. found that symptomatic individuals who avoid dairy foods do not typically self-select to replace the dairy food with other nutrient rich options [19]. Rather, the participants had persistent dietary gaps in essential micronutrient intake, notably for calcium, vitamin D, and magnesium. Dairy food avoidance was associated with a 30% increase in physician-diagnosed diabetes and a 40% increase in physician-diagnosed hypertension. Colon cancer risks are also greater when there is inadequate dietary calcium in the diet. In the 2017 Adventist Health study-2 cohort of over 90,000 participants, consumption of dairy foods and adequate calcium was protective against colon and rectal cancers [20••]. Unabsorbed dietary calcium binds potentially harmful fatty acids and bile acids that serve as colon cancer promoters. Based on the literature, the first intervention for LI individuals remains incorporation of low lactose dairy foods into the diet, in the absence of religious preferences or CMA.

The most studied approach to the clinical treatment of LI is symptom reduction. According to Hertzler et al., LI symptoms and the rise in breath hydrogen does not usually begin until 6 g of lactose have been consumed [21]. When challenged, LI individuals were typically able to consume up to 12 g (i.e., 8 oz of milk) in one serving with minimal or no symptoms [22]. Key steps to improve dairy consumption with reduced symptoms are outlined in Table 3. In clinical practice, dairy foods consumed as part of a meal are better tolerated than the same foods

Table 3. Strategies to Improve Dairy Food Consumption. REF: [1••, 29, 30]

Strategies to Improve Dairy Food Consumption	
Consume dairy with a protein/fat-containing meal	Consume flavored dairy beverages
Start small (5 grams) then gradually increase	Consume low lactose containing foods
Begin with cooked milk in foods	Consume multiple small servings/day
Consume prebiotics	Consume dairy free foods
Consume dairy consistently	Add Lactase enzyme
Add a probiotic daily	Consider A2 milk

consumed on an empty stomach. Protein and fat intake slow the transit time increasing the exposure time that the brush border cells have for reducing lactose to the absorbable sugars, glucose and galactose. It is recommended to begin with ½ cup of milk (5–6 g of lactose) per day in baked foods or with a meal to train the gut to absorb lactose. Over 3–4 weeks, most LI individuals, including minorities, are generally able to consume 4–6 oz of milk with meals three to four times per day with few or no symptoms. Low lactose-containing foods such as yogurt, aged cheese, fermented dairy foods, and lactose hydrolyzed milk, when added to the diet improve health outcomes, in particular for minority patients [25, 26]. Yogurt produces fewer symptoms than milk, despite equal amounts of lactose because live cultures in the yogurt contain bacterial lactase and pre-digest lactose. Therefore, yogurt or yogurt-based drinks should be encouraged early as part of re-introducing dairy foods into the diet [27]. In a pivotal study performed in 1989, Lee and Hardy [28] demonstrated less LM on breath hydrogen study and fewer clinical symptoms with improved tolerance when volunteers consumed chocolate milk versus unflavored milk. The difference in tolerance was attributed to effects from the sugar and cocoa which favorably alter intestinal transit. Murphy et al. demonstrated that consuming flavored beverages did not lead to obesity in children [29]. In fact, children that consumed flavored dairy milk beverages self-selected to reduce their intake of sugary beverages such as soda. Lactase enzyme replacement is also beneficial for individuals with symptoms and varies in its form as outlined in Table 4 [30].

Table 4. Lactose-free or Lactose Reduced Options. REF: [28]

Lactose Free or Lactose Reduced Options	
Lactase enzyme drops	Add to fluid milk 24 hours prior to consumption, LACTAID® enzyme droplets
Lactase capsules or caplets	LACTAID® enzyme caplets (Take ½ dose prior to the meal and the remaining dose during the meal)
Lactase treated dairy foods	Brand name: LACTAID® milk, ice cream, yogurt
Lactose free dairy foods	Brand name: Fair Life® milk (ultra-filtration)
Lactose reduced foods	Aged cheeses (Colby Jack, Monterey Jack, Pepper Jack, Swiss, Parmesan), yogurt, fermented dairy foods including buttermilk

Cow's milk protein consists of 82% casein and 18% whey protein. Casein is comprised of a group of proteins as opposed to a single protein and beta-casein is the most abundant [23, 24]. In milk from the Holstein breed of dairy cows in North America, Northern Europe, and Australia, approximately 60% of the beta casein is A2 beta casein and 40% is A1 beta casein. This is believed due to a single gene mutation that was passed down over the years to the Holstein cow and other breeds. Prior to the genetic mutation, the Holstein cow produced only the A2 beta casein. Dairy cows from Asia, Africa, and Southern Europe naturally produce milk that is nearly all A2 beta casein. Similarly, sheep, goat, camel, buffalo, and human milk contain nearly all A2 beta casein. In the USA, Europe, and other countries, there has been the introduction of A2 milk from genetically modified cows. According the manufacturers, the A1 beta casein is digested differently and produces symptoms indistinguishable from lactose intolerance. Though widely debated, A2 milk is being marketed as "easier to digest for people who are believed to be lactose intolerant."

Prebiotics are the food ingredient that promotes the growth of the gut bacteria or microbiome by serving as a substrate for essential short chain fatty acid production [31, 32]. When these non-digestible, strain-specific fiber compounds are included in the diet, they provide a food source for lactic acid producing colonic bacteria to grow and provide beneficial effect to the host. The lactic acid colonic bacteria confer a protective effect to the LI host, in part, by digesting lactose. Savaiano et al. performed a placebo (corn syrup) controlled trial using 1.5–15 g per day of highly purified galactooligosaccharide (GOS/RP-G28) to assess the effectiveness of prebiotics in managing LI. Following 36 days of GOS on a dairy-free diet, there was a change in the gut microbiome with an increase in the presence of lactose-fermenting *Bifidobacteria*, *Faecalibacterium*, and *Lactobacillus*. The GOS supplementation was held beginning on day 37 of the trial and dairy foods were re-introduced. There was a 71% decrease in symptoms and a 70% reduction in abdominal pain in LI individuals receiving GOS. The LI individuals experienced a 90% increase in lactose fermenting bifidobacteria and an increase in the lactose fermenting *Roseburia* when dairy foods were reintroduced. *Roseburia* is a species that produces the short chain fatty acid butyrate, which is the preferred nutrient for colonic cells, has anti-inflammatory properties and decreases epithelial permeability [33]. However, after 66 days of non-supplementation, the *Bifidobacterium* population returned to pre-treatment levels.

Probiotics are live microorganisms that when introduced to a host, in adequate amounts, provide a beneficial effect. The most studied probiotic strains in LI are *Lactobacillus bulgaris*, *Streptococcus thermophilus*, and *Bifidobacterium longum*. *Lactobacillus bulgaris* and *Streptococcus* are lactase enzyme producers. *Bifidobacterium longum* produces less hydrogen gas and flatulence in the colon. The use of probiotics in the US diet is based primarily on yogurt intake, but supplement use is increasing [34]. In clinical practice, early discontinuation is the main cause for ineffectiveness. In a study by Almeida et al. [35], it took 4 weeks of consistent yogurt consumption to see a beneficial effect on the gut biome. The effect persisted for 3 months after probiotic cessation. Other studies have shown different results in effectiveness, which is thought to be related to the strain of bacteria used and vehicle used for the probiotic [36].

Lactase enzymes are commercially available as a supplement. In most markets, lactase-supplemented foods such as milk, yogurt, and ice cream are also available

[37]. Some dairy farms have changed the methods of processing the cow's milk resulting in ultra-filtered milk, which is better tolerated by many individuals. The ultra-filtered milk is lactose free with 50% more protein and 30% more calcium. The milk contains less water leading to concentrated milk solids and a mouth quality of whole milk but with half the sugars and fewer calories (see Table 2) [38].

Cow's milk protein allergy

Under normal circumstances, antigen-presenting cells in the lining of the gut and barrier mechanisms regulate interactions with specific food antigens. There are immunologic barriers such as secretory IgA and antigen interactions with the T cells of the gut associated lymphoid tissue (GALT). There are non-immunologic mechanisms such as the mucosal barrier of the gut, gut motility, mucus secretions, and intestinal enzymes. Tolerance to cow's milk protein occurs in childhood when there is sufficient IgG4 antibody to compete for binding of the food allergen before it attaches to IgE and triggers an adverse reaction. This allows for immunization to and absorption of the antigen [39]. In addition, increased levels of anti-inflammatory cytokine IL-10, upregulation of allergen-specific T regulatory cells and antibodies to the free light chain of the IgE antibody released during the "activation" phase help to down-regulate the allergic reaction. Tolerance occurs in 60–80% patients by age 16 years of age. Otherwise, it is unlikely to do so. Classic CMA results when there is an allergic reaction or inflammatory response to the milk proteins. The reaction to the milk protein complex can be to a singular component protein or to multiple protein subunits of the casein and whey proteins.

CMA is one of the few indications for dairy avoidance. In the pediatric population, CMA is often milder and self-limited. In adults, CMA are more severe, associated with other immunologic conditions such as asthma or celiac disease, tends to be lifelong and are more likely to be associated with life-threatening reactions such as anaphylaxis. Gastrointestinal symptom associated with anaphylaxis include nausea, vomiting, dysphagia, abdominal pain, diarrhea, and bloody stools [40]. Once the CMA resolve and tolerance occurs, these patients can safely reintroduce dairy foods into the diet under the supervision of a trained healthcare professional [41, 42]. Conversely, adults with chronic atopic conditions were more likely to have one or more food allergies. In a 2019 survey of 40,443 adults [43], approximately 10.8% have symptoms consistent with a food allergy as evidenced by the report of objective symptoms associated with IgE-mediated food allergy. CMA was the second most common allergy reported in 1.9% (1.8–2.1%) of the adults. The peak prevalence for CMA varied by age and was greatest for adults 18–29 years. Upon further analysis, the presence of CMA was more common in ethnic and racial minorities as compared with non-Hispanic Whites (11.2–15.9% versus 10.1%) and was found more often in women versus men (13.8% versus 7.5%). Among adults with asthma, the prevalence of food hypersensitivity is significantly greater (53.1% versus 29.8%) compared with adults without asthma [44].

Notably, up to 65% of patients with IBS report food allergies and hypersensitivities including CMA. Upon testing, there were also increased levels of IgG4 to common food allergens but there was a lack of association with GI symptoms [45]. The milk proteins, lactoferrin and transferrin, have key regulatory

roles in iron absorption and transportation. In addition to iron absorption and transport, lactoferrin appears to have antibacterial, antiviral, and antifungal properties. Excessive loss of lactoferrin in the stool is a surrogate marker of intestinal inflammation [46, 47].

The high phosphate content of the casein allows for more calcium to be naturally concentrated in milk as compared with calcium in solution alone. The bioavailability of calcium makes casein a good source of dietary calcium and protein. The κ -casein in dairy foods contains phenylalanine. However, in the processing of cheese, the κ -casein is cleaved between certain amino acids producing a nearly phenylalanine-free protein, called milk glycomacropeptide, which can be used as a source of dietary protein in phenylketonurics [48]. Baked milk in foods appears to be less allergenic, which may explain why up to 70% of CMA patients tolerate milk proteins in baked goods and yogurt, but not fluid milk. Caseins are heat stable and are generally not affected by high temperature. In contrast, the whey proteins are more sensitive to heat and tend to denature when heated above levels required for pasteurization. The functional, heat-induced conformational changes result in a creamy food texture and are beneficial in the processing of certain foods such as yogurt [49, 50]. Allergy to fluid cow's milk versus baked cow's milk should be assessed for separately to avoid over-restricting the diet [51–53].

There are three types of milk allergies: IgE-mediated, non-IgE-mediated, and mixed IgE-/non-IgE-mediated reactions with evidence for eosinophil activation in some patients [54, 55]. With advances in the management of asthma, there are new biologic therapies that prevent activation of the eosinophil [56]. Given that CMA and asthma share similar inflammatory pathways, these novel treatments are being considered for severe CMA. These new treatment options are limited to experimental use in pediatrics but are increasingly being considered for adults with life-threatening food allergies [57, 58]. While a detailed description is beyond the scope of this section, the most common GI presentations associated with CMA are reviewed.

IgE-mediated reactions are immunologic responses that occur due to food-specific antibody formation causing an allergic reaction typically within 24 h of ingestion (i.e., “immediate hypersensitivity reactions”) [59]. During the initial stage called “sensibilization,” the food allergen is ingested and IgE antibodies develop resulting in sensitizing of the body to the specific food allergen. Subsequent exposures to the same food allergen trigger the release of the IgE antibody causing rapid unleashing of inflammatory mediators, activation of basophils, stimulation of mast cells to secrete histamine, and other mediators of the allergic reaction, known as the “activation” phase. Clinically, mast cell activity can be determined indirectly by measuring the size of a wheal induced by allergen exposure after a skin prick test. Basophil activation is determined by measuring levels of released mediators such as histamine or the upregulated degranulation-associated cell-surface proteins (CD_{203c} or CD₆₃). Acute symptoms occur within minutes to hours after contact with the offending agent, may involve any organ system, and range from mild- to life-threatening anaphylaxis. Some individuals can develop anaphylaxis when exercise follows the ingestion of certain food allergens, including cow's milk protein, which is thought to be related to allergen-induced histamine release. Increased gut permeability and an

impaired intestinal mucus membrane have also been associated with the increased risk of food allergies in childhood [60]. Because gastric acid is required to digest large proteins and eliminate food-borne allergens, some authors have raised concerns about administration of proton pump inhibitors, especially in children, as they have been implicated in the development of food allergies. Infants that receive prebiotics have a lower incidence of atopic dermatitis and food allergies. The effect of proton pump inhibitor therapy and prebiotics in food allergy development in adults is unclear [61].

Non-IgE-mediated reactions are characterized by the onset of symptoms beginning days to weeks post exposure (i.e., “delayed hypersensitivity” reactions) [62] and are associated with negative skin prick tests as well as normal IgE antibody levels. These reactions are mediated by T helper 1 cells, other T cell interactions, mast cells, and neurons that control the function of the smooth muscle and intestinal motility. Non-IgE-mediated reactions presents with symptoms involving the skin, gastrointestinal tract, and respiratory tract, with GI symptoms being the most common. Feuille et al. [63] have postulated that the T cell activation results in local inflammation, increased permeability and fluid shifts at the level of the gut mucosa. The most severe form of this reaction is seen in the first 6–12 months of life in the clinical syndrome known as food protein-induced enterocolitis syndrome (FPIES). Allergic proctocolitis is a milder form also seen in the pediatric population. Both syndromes cause bloody diarrhea. Cow’s milk can also affect the small bowel mucosa causing a syndrome known as cow’s milk-sensitive enteropathy or food protein-induced enteropathy that mimics celiac disease in children. In 65% of cases, CM or soy is the offending food. There are recent reports of similar clinical syndromes in adults with persistent CMA [64, 65].

Mixed IgE- and non-IgE-mediated reactions may present with acute or chronic symptoms. CMA is the second most common allergy reported in this population [66]. More common in the adolescent and adult population are allergic eosinophilic conditions such as eosinophilic esophagitis and eosinophilic gastroenteritis. Adults with eosinophilic esophagitis are more likely to present with dysphagia, recurrent food impactions, chest pain, upper abdominal pain, and reflux symptoms that may or may not respond to proton pump inhibitor therapy. Endoscopic findings include a normal appearing esophagus, furrowing, white plaques, luminal narrowing, and/or focal stricture. Mucosal biopsies containing 15 or more eosinophils per high power field are required to confirm the diagnosis. Treatment may include dietary elimination of milk as part of the six-food elimination diet (i.e., milk, egg, soy, wheat, peanut/tree nut, and fish/shellfish), in addition to proton pump inhibitor therapy and topical steroid use [67–69].

Eosinophilic gastroenteritis is a rare condition that typically involves eosinophilic infiltration of the stomach and the proximal small intestines but may extend from the esophagus to the distal small bowel and colon. It can occur at any age but has a peak onset in the third decade of life with a slight male predominance. Adults are typically between 20 and 50 years of age. The clinical presentation is dependent on the site involved and the degree of inflammation. It is a chronic disease with waxing and waning symptoms requiring a high index of suspicion to

diagnose. Adults may present with nausea with vomiting, abdominal pain, diarrhea, dysphagia, bowel obstruction, cecal mass, intussusception, a volvulus, or an acute abdomen. There may also be eosinophilic ascites and peripheral eosinophilia. Diagnostic criteria require the presence of gastrointestinal symptoms, eosinophilic infiltration of the tissues, exclusion of parasitic activity, and the absence of systemic disease. Mucosal disease presents with fecal protein loss based on the fecal alpha 1-antitrypsin test and steatorrhea with low serum immunoglobulin levels except an elevated IgE. Subserosal disease presents with ascites and profound eosinophilia. The endoscopic findings are non-specific but can be normal. Most often, there is non-specific inflammation with ulcerative changes on biopsy. Endoscopist should take a minimum of 6 biopsies from normal and abnormal appearing mucosa to confirm the diagnosis as the eosinophilic infiltration is often patchy. Initial therapy is the six-food elimination diet for 4 to 6 weeks. Prednisone and immunosuppressant agents such as Azathioprine may be prescribed to treat refractory or recurrent symptoms [70–73].

Studies are in progress to find ways to induce permanent tolerance to food allergens. The food allergen-specific therapies include oral, sublingual, and subcutaneous immunotherapy. Food allergens are modified to retain their ability to induce tolerance but modified to reduce the inflammatory response. Oral desensitization uses small but graduated quantities of an allergen to induce tolerance while minimizing the allergic reaction. Both native foods and modified food proteins have been used to reset the threshold at which a person has a reaction. Recent studies have assessed the combination of anti-immunoglobulin E therapy such as Omalizumab with oral immunotherapy/desensitization for IgE-mediated CMA with a significant decrease in the frequency and severity of reactions. In the small number of trials, there was an increase in the threshold of tolerance to the food allergen. This approach is not curative but may prevent a severe reaction with accidental ingestion of the food specific allergen. Adverse reactions are less severe but remain common [74–76].

Sublingual immunotherapy uses escalating doses of food extracts in the form of liquid drops or a tablet to induce tolerance. The frequency of systemic reactions is less but the rates of desensitization were mixed varying from 16 to 83%. Although the studies consistently reported desensitization, heterogeneity in study design, protocol, and clinical outcomes limit clinical application of this method [77]. Epicutaneous immunotherapy employ a patch-based delivery system that allow for the absorption of graduated doses of the allergen into the body. It has been studied in children with eosinophilic esophagitis who have severe CMA. In the pilot study, this less invasive delivery method was better tolerated despite localized cutaneous adverse reactions in the treatment group. Notably, there was no anaphylaxis reported and no participant required epinephrine. The treatment was well tolerated but there was no significant increase in tolerance. The study duration was 3 months which may have affected their study outcomes [78]. More recent studies have successfully used this approach to address peanut allergies. Subcutaneous immunotherapy has been used but severe systemic allergic reactions

were common preventing widespread application. This approach for management of food allergies has largely been abandoned [79, 80].

Summary

Lactose intolerance and CMA are two clinical conditions that affect a substantial number of patients that seek medical advice and meaningful clinical solutions. However, they remain under-diagnosed and often, untreated. Objective confirmation of the diagnosis is recommended prior to treatment. There are evidence-based dietary interventions that allow for the inclusion of dairy foods in the diet for those individuals with LI to avoid the unintended consequences associated with dairy avoidance. Dairy food consumption remains the first-line management in the treatment of LI given the health benefits, especially for minority patients. Because CMA is a true allergy, early detection is key as dairy avoidance is necessary. Individuals with CMA should also be evaluated for and prescribed epinephrine, when clinically appropriate given the increased frequency of anaphylaxis in adults. Fluid milk versus baked milk allergies should be assessed separately to avoid over-restriction of the diet. While dairy food elimination is the current treatment of choice for CMA, new strategies that employ biologic therapies are emerging as potential treatment options in the future. Supplementation of the micronutrients and vitamins found in dairy foods is recommended when dairy intake is inadequate or avoided.

Compliance with Ethical Standards

Conflict of Interest

Jeannette Keith declares that she has no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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