

# Nutritional Implications of Mast Cell Diseases

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**I**NCREASED RECOGNITION OF mast cell diseases (MCDs) and the role of mast cells (MCs) on physiology has generated great interest in the intersection of MC activation (MCA) and the field of nutrition. MCs are white blood cells that interact with the surrounding environment in organs (ie, lungs, skin, mucosa, and intestines) and connective tissue to regulate inflammation.<sup>1</sup> They play important roles in digestion, allergic reactions, dermatologic diseases, and immune function. When an invader is detected, MCs degranulate, releasing mediators such as histamine, cytokines, leukotrienes, prostaglandins, and heparin.<sup>1-3</sup> These mediators amplify the body's immune response by recruiting additional cells to the affected area. When MCs degranulate in response to a pathogen, the response is protective; however, in disease pathology, ongoing and/or excessive activation of MCs can lead to chronic inflammation, a range of systemic symptoms, allergic and/or autoimmune diseases, and even anaphylaxis (Figure 1).<sup>1,3,4</sup> Understanding the complex involvement of MCs in infections such as SARS-CoV-2 is still nascent and the subject of significant interest.<sup>5-7</sup>

MCs play a crucial role in regulation of peristalsis and nociception, modulating vascular and epithelial permeability, and maintaining the mucosal barrier in the gastrointestinal tract.<sup>4</sup> The influence of aberrant MCA within the gastrointestinal tract can result in symptoms ranging from nausea and vomiting to pain, bloating, and diarrhea following exposure to a trigger.<sup>4</sup>

This article provides background regarding MCD diagnostics, ways MCD influences physiology, digestion, and nutritional status, and the current medical nutrition therapy recommendations. Although frequently conflated,

MCD and histamine intolerance (HIT) are separate conditions. This article compares the two, and enables nutrition and dietetics practitioners to support patients with a suspected or confirmed diagnosis of MCD.

## DIAGNOSIS AND MANAGEMENT

Clonal MCDs are characterized by defined genetic mutations, and include cutaneous, systemic and advanced systemic mastocytosis, and MC leukemias.<sup>1,8</sup> Mast cell activation syndrome (MCAS) is identified by symptoms of MCA, assessment of mediator release, and therapeutic response to medication. Symptoms include severe allergic reactions or anaphylaxis due to the mediators released by MC degranulation or excessive MCA.<sup>8,9</sup> A differential diagnosis should be performed to rule out other diseases that present similarly.<sup>8,10</sup> While ruling out other conditions, criteria for MCAS can be evaluated. Hereditary alpha-tryptasemia (HαT) is a genetic condition characterized by increased baseline tryptase levels that can be accompanied by increased MCs in the small intestine and innate and adaptive immunologic differences that separate HαT from other gastrointestinal diseases.<sup>8</sup> Although there is debate, people with HαT may be more likely to also have an MCD.<sup>8</sup> There is currently limited research specific to cutaneous, systemic, advanced systemic mastocytosis, MC leukemias, and HαT, but it is likely that similar nutrition principles apply to people with these conditions.

There are 2 sets of diagnostic criteria for MCDs, confusing both clinicians and patients. The European Union/US consensus defines MCAS as a syndrome characterized by severe, recurrent, systemic reactions, frequently in the form of anaphylaxis.<sup>9,11</sup> Another group of health care practitioners developed the Consensus-2 guidelines.<sup>12</sup> These have some similarities to the European Union/US consensus, but with broader diagnostic criteria, including some that lack specificity.<sup>12</sup> Due to the inability to

meet diagnostic criteria, patients may be told they have MCA, MCA unspecified, MCA disorder, or MCD.<sup>1,10,13</sup> A study of 266 German volunteers suggests that MCAS may be common, affecting up to 17% of the general population.<sup>14</sup> Treatment of MCD is typically targeted to reduce symptoms, utilizing antihistamines, leukotriene inhibitors, antiprostaglandin therapies, and MC stabilizers.<sup>1,10</sup> Patients may have symptoms of MCA without having an MCD, and may benefit from these medications as well.

Diagnosis is outside of the scope of practice of a registered dietitian nutritionist (RDN). The role of RDNs is to notice potential signs of an MCD and make appropriate referrals. For patients with a diagnosed MCD, an RDN can help expand the diet, encourage nutritional adequacy, identify potential triggers, discuss ways of enhancing food tolerance, consider supplementation for nutritional adequacy or to downregulate MCD reactions, screen for disordered eating, and participate in the eating disorder treatment team when appropriate. Patients suspected of having an MCD should be referred to their primary care provider or an allergist/immunologist for evaluation. More information regarding testing or education for providers can be obtained from The Mast Cell Disease Society ([www.tmsforacure.org](http://www.tmsforacure.org)). The rest of this article addresses the dietary treatment of people with MCAS, MCA, and suspected MCAS collectively under the umbrella term MCD, but may be helpful for patients with other MCDs as well.<sup>1,8-14</sup>

## COMPARISON OF MCD AND HIT

MCD and HIT are often confused. HIT is the impaired ability to metabolize histamine from foods, whereas MCD can sometimes result from MCs releasing a multitude of mediators.<sup>1,15,16</sup> Symptoms of HIT overlap with MCD, including hives, urticaria, bloating, postprandial fullness, diarrhea, and

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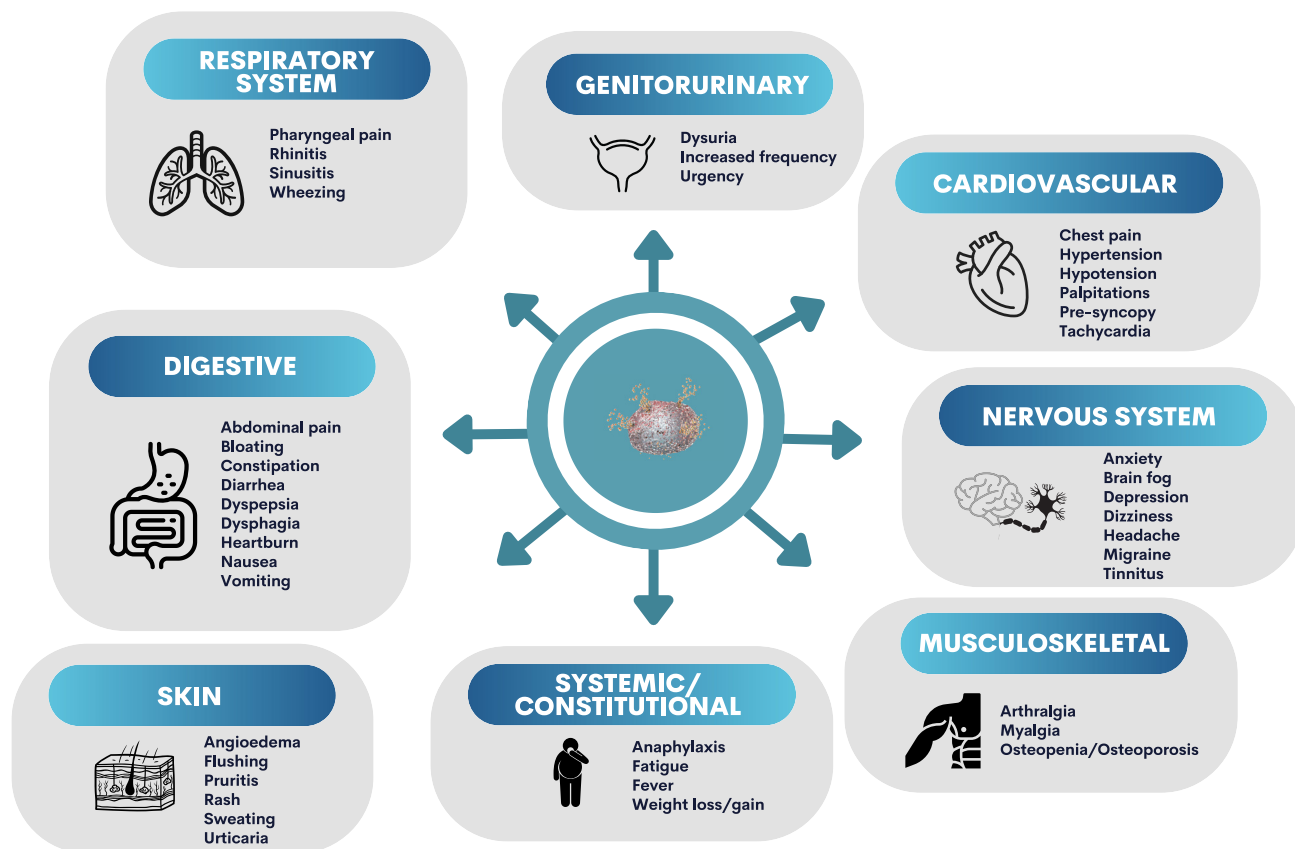


Figure 1. Symptoms of mast cell disease.<sup>9–11,17,22</sup>

migraine, among others.<sup>17,18</sup> The hypothesized cause of HIT is a deficiency in the diamine oxidase (DAO) enzyme, which degrades histamine.<sup>19</sup> Reduction of DAO enzyme presence or activity can be a result of genetic variability due to occurrence of single nucleotide polymorphisms, intestinal injury, malnutrition, and/or diseases influencing the brush border where DAO is produced. Some medications can reduce activity of DAO.<sup>15,20</sup> In addition, DAO activity may be influenced by body mass index, sex, and age.<sup>21</sup>

Diagnosis of HIT can be challenging and is often based on symptoms due to lack of an identified biomarker.<sup>20</sup> Because symptoms are caused by an overload of dietary histamine or the inability to degrade it, treatment of HIT is a combination of a low-histamine diet (LHD), DAO supplementation, and the reduction of alcohol intake and DAO-depleting medications if possible.<sup>15,16,20</sup> DAO supplements have not been studied in people with MCD and are not believed to be therapeutic for this population.

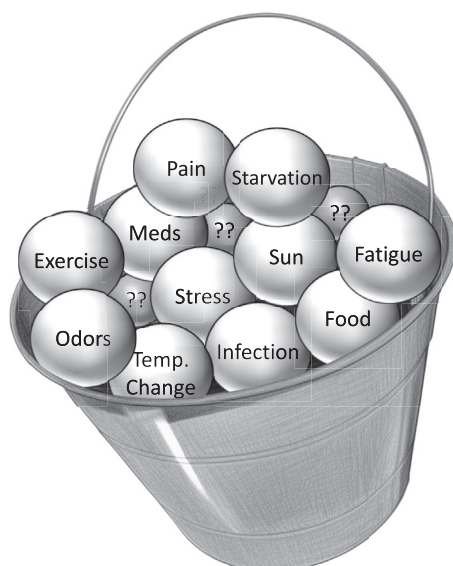
### MAST CELL PHYSIOLOGY

MCs are immune cells that function as a primary line of defense against bacteria, viruses, and other potential pathogens.<sup>1</sup> Activation of MCs can be due to either immunoglobulin E (IgE) or non-IgE mediated responses, involving cutaneous, respiratory, digestive, cardiovascular, and/or neurologic systems, and potentially including anaphylaxis.<sup>23,24</sup> For some patients, MC reactions are physiologic responses to many triggers, including ingested substances (eg, foods, drinks, and medications).<sup>17,23,24</sup> MCs have a plethora of surface receptors that respond to a wide range of stimuli, which may account for variability in the presentation of MCA.<sup>22,25</sup> This varied response can be dependent on external factors, such as the physical environment, chemical exposure, or circadian rhythms.<sup>3,17,24,26</sup> Internal factors such as stress, infections, hormones, altered microbiome, bacterial overgrowth, and a myriad of immune and inflammatory stimuli can also play a role.<sup>22,27,28</sup> In addition, the quantity

of a trigger food ingested and other meal components can also influence the likelihood of MC degranulation.<sup>29</sup> Regardless of how MC degranulation is triggered, via IgE-dependent signaling or non-IgE-mediated signaling, the clinical outcome is indistinguishable.<sup>30</sup>

### MAST CELL TRIGGERS

MCD is a unique disease; no 2 people will have identical triggers.<sup>17</sup> Factors that provoke MC reactions vary widely and include physiological stimuli, ingested items, environmental exposures, and psychological reactions.<sup>1,17,31,32</sup> A study of people with a range of MCDs found high environmental temperature was the most commonly reported trigger (82%), followed by stress (81%), physical exertion (63%), ingested alcohol (54%), medications (53%), food or beverages (50.3%), odors (48%), and insect stings (35%).<sup>31</sup> According to a separate survey, 41% of people reported limiting their consumption to 20 foods or fewer to avoid



**Figure 2.** Potential triggers for mast cell disease reactions.<sup>17,31,33</sup> Temp = temperature.

symptoms of MCA.<sup>17</sup> Although food is a common self-assessed trigger, only 10.7% of people with MCD report receiving a physician's referral to an RDN.<sup>32</sup>

Recent efforts have been made to address the heterogeneity of responses to specific triggers, including temperature, physical exertion, consumption of alcohol or histamine-containing foods, stress, sleep deprivation, and starvation.<sup>33</sup> Based on reactivity to these triggers, patients were classified into 3 groups: high, intermediate, and low responders. High responders reacted to all triggers, intermediate responders were not triggered by cold temperatures, and low responders were largely unresponsive to these triggers, with the exception of stress. Further analysis revealed associations between abdominal complaints and consuming more histamine, dermatological symptoms and physical exertion, neurological symptoms and physical exertion or starvation, and cardiac symptoms with diverse triggers. These differences could not be accounted for by measuring MC-associated mediators.<sup>33</sup> This study supports implementation of an individualized approach for patient success, including a detailed review of triggers and symptoms (Figures 1 and 2) with evaluation of effect of modulating individual factors (eg, exercise and specific foods) and providing a customized plan for the patient.

### DIETARY PROTOCOLS FOR MCD

In a survey of people with MCD, about half of respondents reported reactions to foods and beverages.<sup>31</sup> Common triggers include vegetables (29.5%), fruit (27.3%), dairy (26.7%), grains (24.4%), shellfish (23.9%), food additives (21.6%), alcohol (18.2%), fermented foods (6.3%), leftover foods (2.3%), and high histamine foods (1.7%) (Figure 3). Although few respondents identified high-histamine foods as offending, the nonspecific general category of higher-histamine foods may include items in other categories (eg, some vegetables, fruits, alcohol, fermented foods, and leftovers).<sup>31</sup> Further research is needed to understand the nature of reactions to these foods in patients with MCDs.

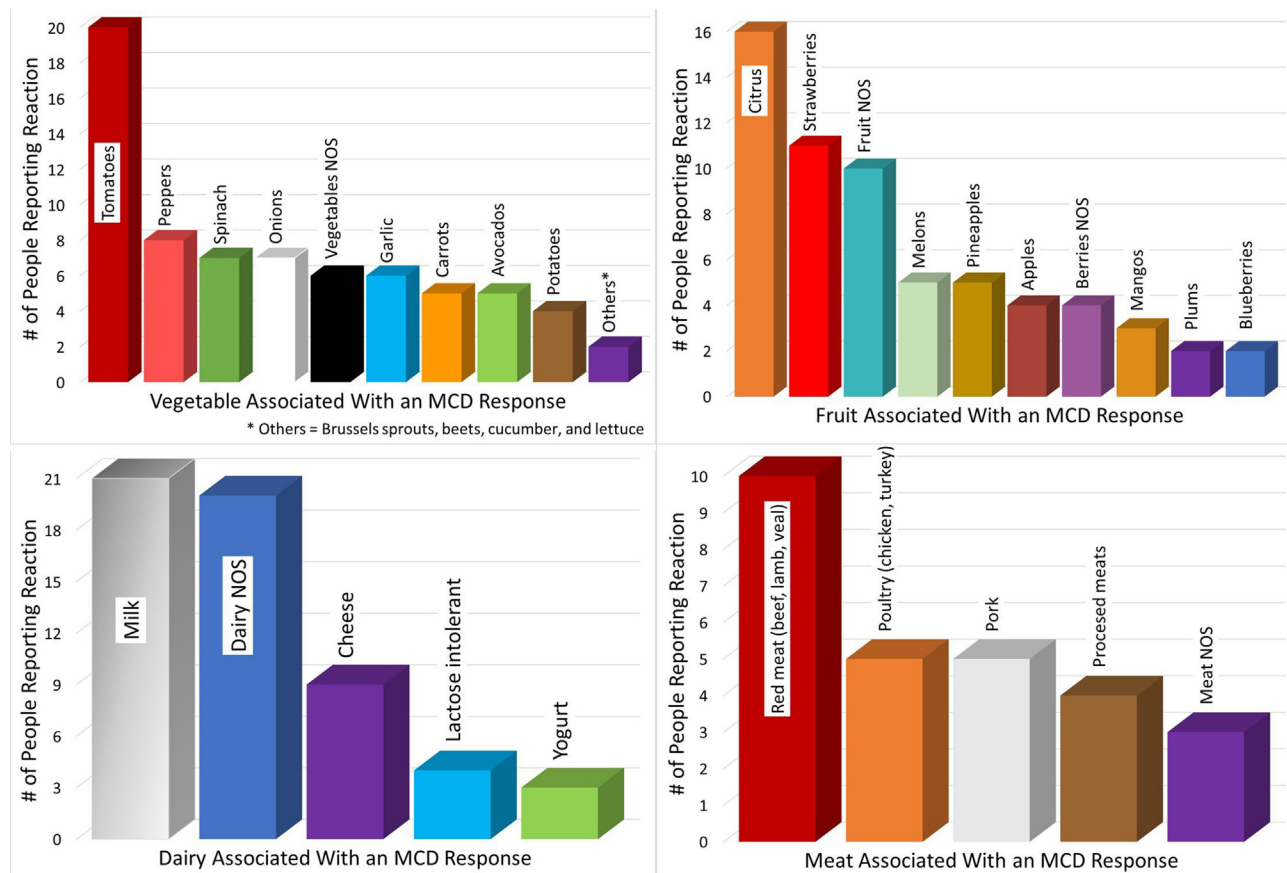
Recommendations for foods to eliminate are based on several self-reported studies on MCD and/or clinician observations. The 2 most utilized elimination/reintroduction diets for MCDs are an LHD and a low Fermentable Oligosaccharides, Disaccharides, Monosaccharides, and Polyols (low-FODMAP) diet. Broadly, an LHD consists of fresh foods and avoids fermented and aged foods. The lowFODMAP diet is a 2- to 6-week elimination diet with decreased amounts of osmotically active short-chain carbohydrates.<sup>34</sup> All elimination diets should be followed by a reintroduction phase.<sup>35,36</sup>

Despite the general consensus that diet influences MCDs, there is little published research. The Mast Cell Disease Society survey mentioned above is the only 1 to analyze reported MCD food triggers and implicates a wide range of foods. Milk, tomatoes, citrus, onion, garlic, and processed meat align with either high histamine and/or high FODMAP food lists. However, other triggers, such as blueberries, melon, carrots, potatoes, meat, and chicken, do not.<sup>13,37</sup> Randomized studies are needed to examine which dietary principles help a majority of people with MCD.

In practice, clinicians find that MC triggers are highly individualized. Patients often seem to benefit from avoiding processed foods which typically contain additives and preservatives.<sup>13,31,38</sup> Limited evidence indicates that dyes in food and medications and aspartame may also be MC irritants.<sup>39,38</sup> Clinicians should emphasize finding the widest range of foods that patients tolerate.

Interventions include changing food preparation or storage methods and introducing dietary modifications when appropriate. Broad elimination of entire categories of food is not recommended. No evidence supports such an approach, and studies show the potential harm of overrestriction, malnutrition, and/or deficiencies.<sup>35,40,41</sup> When patients report symptoms due to specific foods, nutrition and dietetics practitioners should consider a 4-week elimination of suspected foods, followed by a reintroduction of the foods 1 by 1 or by FODMAP group to determine individual tolerance.<sup>13,35,40</sup> The goal should be as wide and varied a diet as tolerated. This process may involve experimenting with type of food and amount, all while monitoring the cumulative load of individual MC triggers, such as stress, environmental temperature, and physical activity. Often if the patient can decrease their cumulative external triggers or add in additional support through medications, supplements, stress management, and so on, a greater variety of foods can be tolerated (Figure 2).

An RDN and the patient must collaborate to develop an individualized treatment plan to determine which foods are tolerated and how much, which can be challenging and



**Figure 3.** Self-reported mast cell disease (MCD) food triggers according to The Mast Cell Society (TMS) survey.<sup>31</sup> NOS = not otherwise specified.

nuanced. If symptoms return when a food is reintroduced, the food is likely a trigger in the quantity and/or form consumed. The method of food preparation may also influence tolerance. For example, studies show boiling foods may reduce levels of histamine or other biologic amines.<sup>15</sup> People with MCD report different levels of tolerance based on factors such as cooking, freezing, method of preparation, and different brands.<sup>17</sup>

### HISTAMINE IN THE FOOD CHAIN

Histamine triggers MCs to degranulate, releasing a cascade of mediators, including more histamine. As animal protein degrades, free histamine content increases by breaking down the amino acid histidine into histamine.<sup>18</sup> It is common for patients to report symptoms with consumption of animal protein leftovers due to these higher histamine levels, even with proper food handling.<sup>36</sup> Immediately freezing leftovers and thawing just

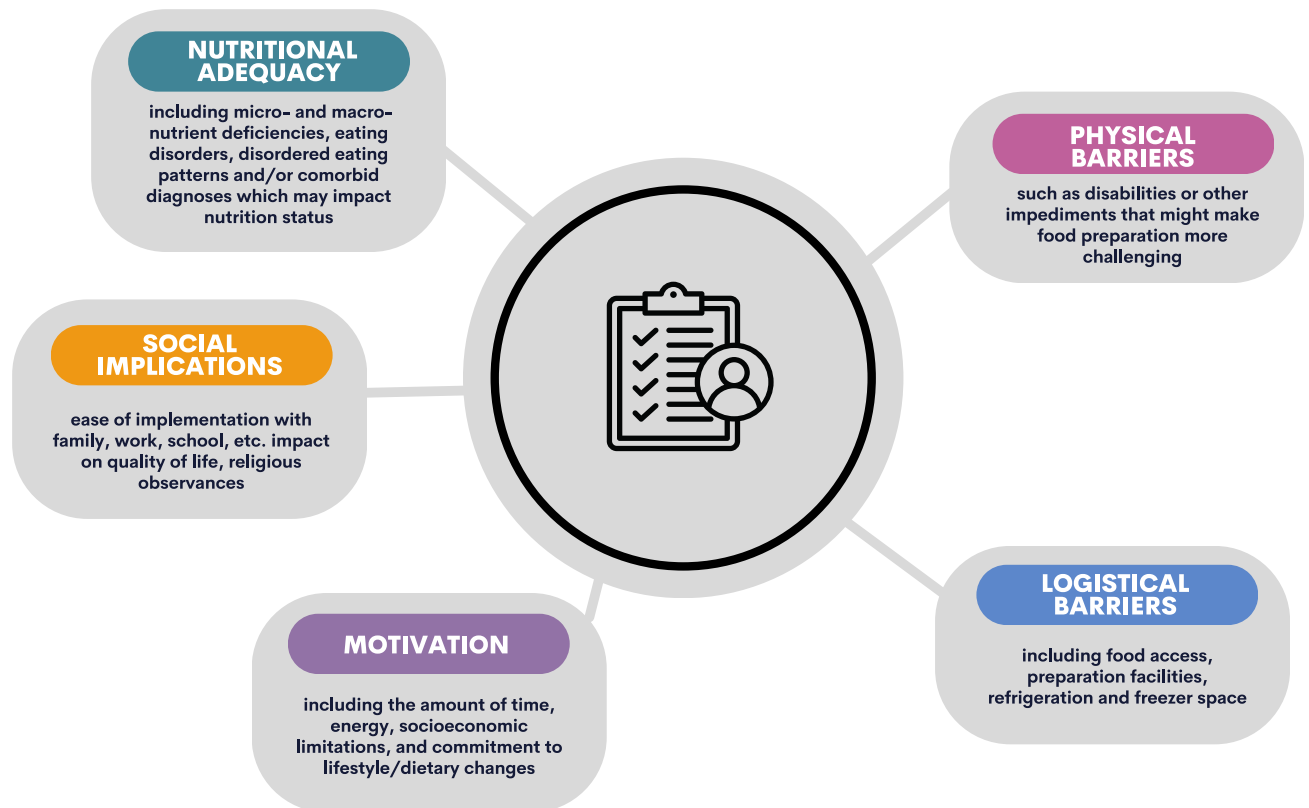
before consumption may decrease symptoms associated with histamine intake.<sup>36</sup> Foods with high histamine content, such as wine, particularly red wine, aged cheese, fermented foods, sausages, and smoked/cured foods are potential triggers, although not all patients with MCDs react to all high-histamine foods.<sup>36</sup>

### A Low Histamine Diet

Histamine content of foods varies greatly because it is based on the amount of naturally occurring histidine, and any microbial contamination introduced during food processing or storage. Currently there is no evidence-based consensus of high- and low-histamine foods.<sup>16,37</sup> An LHD is frequently prescribed by practitioners despite the lack of evidence. Studies indicate the majority of histamine is released by MCs or basophils, with approximately a 5% contribution from

food or gut microorganisms.<sup>42</sup> There are no experimental studies examining an LHD in patients with MCD.<sup>43</sup> A 2018 survey conducted by The Mast Cell Disease Society asked patients with MCD to self-report their experience with an undefined LHD. Of the patients who reported following an LHD, 51.1% reported an improvement in symptoms, 19.1% reported that an LHD did not improve symptoms, and 29.8% were unsure.<sup>32</sup> Despite the known shortcomings of self-recorded dietary reports from individuals, they provide useful information at the patient population level.<sup>44</sup>

Investigation of the efficacy of an LHD is warranted given the number of patients reporting positive outcomes when following an LHD, preferably through a blinded, placebo-controlled trial.<sup>37</sup> This would enable clinicians to better evaluate the potential utility and shortcomings of an LHD in people with MCD.



**Figure 4.** Factors determining nutrition therapy readiness for people with mast cell diseases.<sup>40</sup>

### A Low FODMAP Diet

Another potential dietary strategy for MCD is a low FODMAP diet. A low FODMAP diet is a therapeutic nutrition intervention that oftentimes is misconstrued as an elimination-only diet; however, the structured re-introduction phase is essential. The low-FODMAP diet is best administered under the careful supervision of a specially trained RDN.<sup>35,40</sup> Although there are no studies of low FODMAP diets in people with MCDs, data can be extrapolated from studies on irritable bowel syndrome (IBS) and other digestive disorders.<sup>45–47</sup> The relevance of these findings to people with MCDs is suggested by the increased presence of MCs in patients with IBS and the consideration of MCs as key components in IBS pathophysiology.<sup>45,47</sup> Research indicates that a low FODMAP diet can decrease digestive symptoms for 57% to 82% of people with IBS, with the potential to alleviate symptoms such as gas, bloating, diarrhea, and pain.<sup>34,35,40</sup>

In a study of the influence of a low FODMAP diet on urinary histamine levels, 40 patients with IBS were assigned to low and high FODMAP diet groups. The low FODMAP diet group had a statistically significant eightfold reduction in urinary histamine, in addition to reporting a decrease in IBS symptoms.<sup>48</sup>

Direct influence of a high FODMAP diet on MCs and MCA has been exhibited in rodents. Lipopolysaccharides, barrier dysfunction, and MC presence all increased with high FODMAP diets in both studies.<sup>49,50</sup> After showing that a high-FODMAP diet increased MCA, and barrier dysfunction in the colon, the authors subsequently showed following a low FODMAP diet improved colonic barrier function and reduced MCA. The investigators then demonstrated decreased MCA in a cohort of 6 patients following the low FODMAP diet, suggesting potential benefit of a low FODMAP diet for modulating MCA.<sup>49</sup> Larger studies are needed; however, these studies provide

biologic plausibility for dietary modification to reduce MCA.

### NUTRITION SCREENING

An RDN should assess whether or not a patient is a good candidate for a therapeutic diet before dietary changes are explored. Factors to consider include: 1) nutritional adequacy, including nutrient deficiencies, caloric adequacy, and/or eating disorders or disordered eating patterns and comorbid diagnoses that might influence nutrition; 2) motivation, including the amount of time, energy, socioeconomic factors and commitment; 3) logistical barriers, including food access, preparation facilities, refrigeration, and freezer space; 4) social implications, including ease of implementation with family, work, school etc and influence on quality of life, religious observances, etc; 5) and physical barriers, such as disabilities or other impediments that might make food preparation more challenging<sup>40</sup> (Figure 4).

## Eating Disorders

Patients must be screened for eating disorders or disordered eating patterns before discussing dietary changes.<sup>51</sup> This can be done with an eating disorder screener, such as the Eating Attitudes Test - 26 (EAT-26), the Sick, Control, One Stone, Fat and Food Questionnaire (SCOFF), or the Nine Item Avoidant/Restrictive Food Intake disorder Screener (NIAS), depending on the presentation of the patient.<sup>52–54</sup> There is a well-documented link between digestive disorders and disordered eating, with 23% to 53% of patients with disorders of gut-brain interactions showing symptoms of disordered eating.<sup>41</sup> If disordered eating is suspected, the patient should be referred to a therapist who specializes in eating disorders for further assessment. A potential link between eating disorders and MCD has been suggested by experts, a case report, and work in an animal model.<sup>55–57</sup> A case report proposes that starvation due to anorexia nervosa may trigger MCA.<sup>55–57</sup>

Estimates for prevalence of avoidant restrictive food intake disorder (ARFID), in patients with gastrointestinal disorders vary from 10% to 20% in patients with disorders of gut-brain interactions.<sup>58</sup> Most (43% to 78%) people with conditions such as eosinophilic esophagitis, inflammatory bowel disease, and celiac disease have a positive NIAS screen for ARFID. These conditions are often stressful and involve specific and challenging dietary treatments and constant vigilance around symptoms; these may be the closest analogs to MCD in the current literature.<sup>58</sup> However, a specific diagnostic requirement of ARFID is “when the eating disturbance occurs in the context of another condition or disorder, the severity of the eating disturbance exceeds that routinely associated with the disorder...”.<sup>59</sup> None of the screeners are validated for people with food allergies, digestive diseases, or complex medical conditions such as MCD. All screeners, particularly the NIAS, likely overestimate the risk of eating disorders and disordered eating in people with complex medical conditions like MCD; more specific or adapted tools are needed.<sup>41,58</sup>

Nutrition plans must be carefully tailored, balancing any risk of anaphylaxis or physiologic adverse

reactions to food, but also avoiding unnecessary overvigilance and food anxiety.<sup>60</sup> The goal is always to encourage a diet that allows as wide and varied an intake as possible while maximizing quality of life and minimizing restrictions.<sup>40</sup> Strict elimination plans are not appropriate for patients with eating disorders, and are discouraged for people at risk of relapse.<sup>40,55</sup> Food diaries and recalls may be a trigger for people with eating disorders, so clinicians should use discretion when assessing patients.

A defining characteristic of MCD is that symptoms respond to a range of medications that reduce MC-induced symptoms.<sup>1,10–12</sup> Common medications include H1 blockers, H2 blockers, leukotriene and prostaglandin inhibitors, MC stabilizers, or monoclonal antibodies.<sup>10,27</sup> If an RDN suspects an MCD in a patient who is not a good candidate for a therapeutic diet, referrals may include a knowledgeable physician for a trial of MC medications and a therapist for eating disorder support and coping strategies for managing complex illness. A wider range of foods are generally tolerated with MC stabilizing medications. Dietary changes that feel manageable, such as expanding the patient's diet, shifts in preparation method, the addition of supplements and other potential minor adjustments may be adjunctive support.

## Food Anxiety

Food anxiety is fear and/or avoidance of specific foods that a person associates with a negative outcome. MCD symptoms can contribute to food anxiety, causing overelimination of too many foods and/or entire food groups. Particularly when patients suspect issues with multiple classes of foods (eg, FODMAPs, high histamine, and salicylates), it is not advisable to implement multiple elimination diets concurrently.<sup>35</sup> This would increase the potential for food anxiety and also exponentially increase the risk of malnutrition. Targeting key foods that seem problematic based on diet recall is the initial goal. It is certainly frustrating to modify diets slowly and methodically, but overelimination can have detrimental effects on nutritional

status.<sup>35</sup> When patients express fears about a wide range of foods, an experienced mental health clinician should be included as part of the multidisciplinary team.<sup>40</sup>

It is understandable that patients who are experiencing profound physiologic distress, pain, or anaphylaxis may have anxiety around eating. This can lead to decreased interest in eating, Pavlovian anticipatory reactions, conditioned food aversions, and/or a reluctance to eat.<sup>40,60–62</sup> Empathy, normalizing these reactions, and help planning and identifying coping strategies may be supportive.<sup>63</sup>

## SUPPLEMENTS FOR MCDs

A limited number of supplements have human data indicating potential utility for MCDs. A range of supplements have been researched; however, much of the work was performed in vitro or in animal models. The supplements included here have supportive human clinical data.

Vitamin D is a key player in bone health and immune regulation, and early research indicates that a deficiency of vitamin D contributes to MCA in mice.<sup>64</sup> This has sparked interest in exploring the potential role in human MCA. Vitamin D levels correlate with allergic diseases, including food allergies, atopic disease, chronic urticaria, and asthma in human beings. Paradoxically, both vitamin D deficiency and elevated vitamin D concentrations have been correlated with an increased risk of IgE production and greater risk of food allergy in children. This supports the idea of supplementing to maintain optimal levels while being mindful of oversupplementation because there is potential harm at both extremes.<sup>65</sup>

Flavonoids are naturally occurring polyphenols found in a range of foods (eg, vegetables, fruits, herbs, and spices) and have antioxidant and anti-inflammatory properties. Two that inhibit MC activity are quercetin and luteolin. Preliminary data indicate that both luteolin and quercetin appear as effective as cromolyn sodium at reducing the release of histamine, leukotrienes, and prostaglandin D<sub>2</sub>, and can inhibit cytokine release by human MCs in culture.<sup>45,66–69</sup> Luteolin and quercetin are largely regarded as safe, although there is a caution to keep

total daily flavonoid consumption under 1 to 2 grams daily because of the potential influence on liver metabolism.<sup>70</sup> Much of the research in human beings has been funded by supplement manufacturers. Independently funded clinical trials on polyphenols to attenuate MCA are warranted.

Palmithoylethanolamide (PEA) is a dietary derivative of a component found in egg yolks and peanuts that is theorized to activate natural cannabinoid receptors and downregulate MC receptors.<sup>71,72</sup> Polydatin is a resveratrol compound derived from grapes and hypothesized to stabilize MCs.<sup>71</sup> A recent clinical trial tested the combination of 200 mg PEA and 20 mg polydatin twice daily in comparison to placebo in a 12-week, double-blind study in 54 subjects with IBS who had increased intestinal MC counts. The IBS group receiving a PEA and polydatin combination had significantly lower abdominal pain scores than the placebo group.<sup>71</sup> More study of PEA and polydatin individually and in combination specifically focused on people with MCDs is warranted.

Vitamin C, or ascorbic acid, is often considered foundational for MC support. Although vitamin C is commonly mentioned as an MC stabilizer, human studies are limited to utilization of intravenous ascorbic acid infusions to lower histamine levels in allergic diseases or in vitro models.<sup>73,74</sup> Human studies of oral vitamin C are needed to evaluate the potential utility for patients with MCD.

Probiotics are live microbes that offer a range of health benefits to the host when consumed in a sufficient amount; the doses will depend on the specific strain and intended purpose.<sup>75</sup> They are often utilized in people with digestive symptoms despite mixed reports on efficacy.<sup>76</sup> Individual probiotic strains can quell or amplify inflammation and allergic responses by acting on immune cells, including MCs; the efficacy of specific strains can be enhanced by combining strains and species as well.<sup>75,77–80</sup> Histamine is a signaling molecule in the gastrointestinal tract, and probiotics have the potential to modulate histamine levels.<sup>81</sup> *Lactobacillus rhamnosus* GG (LGG), *L rhamnosus* Lc705, *Propionibacterium freudenreichii* subsp *shermanii* JS, and *Bifidobacterium animalis* subsp *lactis* Bb12, alone and in

combination, influenced expression of a wide variety of gene transcripts that are involved in MCA.<sup>82</sup> LGG and Lc705 suppress genes that encode for IgE receptor subunits and the histamine-4 receptor, downregulate expression of proinflammatory proteins, and upregulate proteins that promote anti-inflammatory functions.<sup>75</sup> In vitro murine studies demonstrate that *Lactobacillus paracasei* CNCM I-1518 prevents IgE-dependent MCA, and studies in human basophils yielded similar results.<sup>83</sup>

Suppression of MCA is strain-specific; however, as demonstrated through the examination of 40 *Lactobacillus paracasei* strains that showed a wide range of MCA inhibiting activity, suggesting that careful selection of strains may be necessary to modulate MCA. Furthermore, there may be a therapeutic benefit to combining probiotics. Combined administration of *L rhamnosus* LR 32, *Bifidobacterium lactis* BLO4, and *Bifidobacterium longum* BB 536 had a therapeutic effect on MCs, modulating the inflammatory cascade and preventing cytokine release.<sup>84</sup> This research should not be extrapolated to mean that all probiotic preparations are beneficial for people with MCDs. Some types of probiotics cause a release of histamine, and studies have shown this is the case for strains such as *Lactobacillus reuteri* ATCC 23,272 and *Lactobacillus saerimneri*.<sup>15,85</sup> Many other probiotic strains are untested and have the potential to be histamine-releasing.<sup>15</sup> More research is needed, especially on people with MCDs.

### IMPORTANCE OF TEAMWORK

Nutrition and dietetics practitioners function optimally within the framework of a health care team. MCDs are complex diseases, potentially influencing nearly every system in the body. Due to common comorbidities such as Ehlers-Danlos syndrome, postural orthostatic tachycardia syndrome, and other forms of dysautonomia, having a broad referral network and an integrated team is important to help patients access needed care.<sup>86–88</sup> When patients present with suspected MCD, it is often necessary to refer to other members of the team to ensure a formal diagnosis and medically appropriate disease management. Patients often need support for diagnosis,

symptom management, and to find experts to diagnose and treat comorbid conditions.

### PUTTING IT INTO PRACTICE

With increasing buzz around dietary histamines and MCs in the press and online, nutrition and dietetics practitioners will see more patients who have suspected MCAS or an MCD and want a plan of action. It is important to have documentation of the long-term implications of MCDs and an understanding of current dietary recommendations. It is critical that nutrition and dietetics practitioners identify potential signs of an MCD and offer dietary protocols that support the patient and allow for a varied intake by utilizing a reintroduction phase with all elimination diets. Diet changes need to be individualized for each patient, and trials need to investigate the potential benefits and harms of a low-FODMAP diet, an LHD, and other dietary strategies. Additional clarification of the role of supplements and the effects of food additives and preservatives in patients with MCDs are needed. It is vital to research MCD and eating disorders, and, potentially, the development of screeners appropriate for complex diseases with digestive symptoms like MCDs. Because symptoms of MCA influence many systems, future studies should include collection of data to evaluate the relationships between nondigestive symptoms of MCA (Figure 1) and nutrition therapies that would help to better guide the practice of dietetics as it relates to MCDs. MC professionals must recognize the importance of referring to RDNs, and nutrition and dietetics practitioners must partner with a network of supportive clinicians to provide patients with comprehensive care.

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