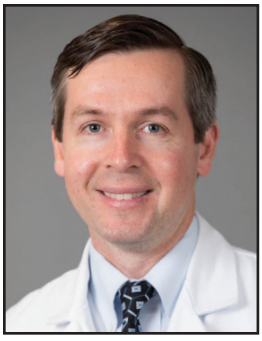
Carol Rees Parrish, MS, RDN, Series Editor

# Mast Cell Activation Syndrome – What it Is and Isn't



Matthew J Hamilton

Kate Scarlata

**Mast cell activation syndrome is a multi-organ, multi-symptom disorder characterized by clinical features and responses to medications that block mast cells. While some laboratory testing can be used to support the diagnosis, there are no diagnostic biomarkers for clinical use, which has hampered clinical care and research. Furthermore, lay literature and social media are outpacing the science, which has led to controversy with regards to diagnostic criteria and treatments. In this review, we will help to explain what mast cell activation syndrome is, and is not, with an emphasis on gastrointestinal manifestations and the therapeutic role of nutrition.**

## CASE PRESENTATION

A 45-year-old female was feeling well until she had the "flu" last winter. She subsequently developed episodic hives and facial flush, cramping abdominal pain, loose stools, fatigue, and palpitations. Many of her symptoms were improved with Benadryl, but were worsened by alcohol, hot showers, fragrances, and various foods and medications. She had an elevated metabolite for prostaglandin on a 24-hour urine collection during one period of symptoms.

## INTRODUCTION

### Mast Cell Activation Syndrome: Why There is Controversy

It has been a decade since idiopathic mast cell activation syndrome (i-MCAS) first appeared in the literature, described as an idiopathic syndrome where other conditions have been ruled out and additional criteria are met (see "what it is" below). Since that time, much progress has been made with regards to understanding which patients fit this diagnosis and stand to benefit from directed therapies.[1] Unfortunately, the lack of validated disease biomarkers and objective testing has hampered the scientific study of the pathogenesis of this disorder; hence many questions remain as to what initiates and perpetuates the syndrome. Furthermore, well designed clinical trials to test new safe and efficacious therapies are difficult to design without objective endpoints and well-defined patient cohorts. The rise of patient self-help groups through social media and an extensive lay literature have given rise to a population of patients who may have chronic symptoms, but likely do not have i-MCAS and therefore may not be receiving the appropriate care.

Matthew J Hamilton, MD Associate Gastroenterologist, Brigham and Women's Hospital Assistant Professor of Medicine Harvard Medical School Boston, MA Kate Scarlata, MPH, RDN Practicing Dietitian Medway, MA

## Mast Cell Activation Syndrome: What it Is

Mast cell disorders are currently classified into "clonal" vs. "non-clonal" disorders. In clonal disorders, there is evidence of a well-defined mutation and resulting aberrant population of mast cells in the tissues. In the "non-clonal" disorder, no such abnormalities have been identified and/or validated.[2] The prototypic clonal mast cell disorder is systemic mastocytosis (SM), which has defined clinical diagnostic criteria and characteristic manifestations - namely a marked increase in the mutated mast cells in the various tissue compartments including the bone marrow, skin, and gastrointestinal (GI) tract.[3,4] Many of the symptoms attributed to mast cell activation in the non-clonal forms are learned from the study of SM patients where there is substantial overlap in non-clonal and SM clinical presentations (e.g. symptoms and triggers of mast cell activation as well as responses to medical therapy to block mast cells).

I-MCAS is the primary "non-clonal" mast cell disorder that may best explain a given patient's clinical presentation without evidence of a well-defined mutation. There are proposed diagnostic criteria that include classic symptoms of mast cell activation in two or more organ systems, such as skin, GI, and airway, refer to Table 1 that are made worse by predictable triggers (e.g. certain foods as discussed below, strong scents, temperature changes, stress, alcohol, certain medications).[5] To confirm the diagnosis of i-MCAS, laboratory evidence in the form of an elevation above baseline in serum tryptase or metabolites of mast cell mediators (e.g. n'methylhistamine, prostaglandin F2-alpha, leukotriene-E4) during a period of increased symptoms should be present. Of note, the duration of increased mast cell activation symptoms may be variable from hours to days to weeks. Patients who are suspected of having i-MCAS, but who do not meet the laboratory criteria, may be considered to have "suspected MCAS." In these patients, trials of directed therapies can continue, but only with ongoing testing for other conditions to better explain the presentation with repeat mast cell mediator testing during periods of symptoms. Studies are underway to determine whether certain features of the mast cells in the various tissue compartments (such as expression of cell surface receptors, protease content, and cell morphology) can serve as diagnostic biomarkers. Traditional biopsy tests (including intestinal) with stains to highlight the presence of the mast cells (e.g. CD117 (KIT), tryptase) have not yielded useful diagnostic information to date.

Since the proposed diagnostic criteria were published, subtypes of i-MCAS have emerged that may require specific therapies and treatments. Patients with i-MCAS may have concurrent anaphylaxis and/or additional conditions, most commonly:

- the hypermobility form of Ehlers-Danlos syndrome
- any form of dysautonomia (namely the postural orthostatic tachycardia syndrome [POTS])
- mast cell activation due to an increased germline copy number of the tryptase TPASB1 gene now termed hereditary alpha-tryptasemia (HAT).[6-9]

The standard approach to treating the symptoms of mast cell activation is outlined in Table 2. Note that initial management in symptomatic patients is similar in all subtypes of i-MCAS.[10] While medications are being initiated and titrated, adjunctive dietary modifications and therapies are instituted. GI symptoms, which are very common in iMCAS and represent a significant portion of the morbidity these patients experience, are largely treatable with this treatment approach.[11.12]

### *Potential Role of Diet in MCAS*

Individuals with mast cell disorders typically have a number of triggers for their mast cell-related symptoms, including dietary factors. In order to better understand their prevalence, Jennings et al conducted an internet-based survey publicized to individuals with mast cell disorders, including SM and MCAS.[1] Among the 420 valid responses (defined as those who answered at least some questions beyond the opening section for demographics and diagnosis), nearly half self-reported "food allergies," yet only 23.2% had positive food allergy tests, indicating that the majority of food-related symptoms in these respondents may be related to mast cell activation itself or indirectly related to mast activation in

the form of food intolerance. Of the 47 survey participants who identified dairy foods as a trigger, 44.7% identified milk, 19.1% cheese, and 6.4% yogurt. Additionally, 43 respondents identified cereal grains as a symptom trigger, with wheat and gluten most commonly cited. In 38 respondents, 34% reported food additives to be triggers such as preservatives (sulfites, benzoates, nitrates); monosodium glutamate and food dyes were also noted. In 32 respondents, more than half identified alcohol, wine more likely than beer, to provoke symptoms. Tomatoes, citrus, and strawberries were the most frequently mentioned produce-based trigger foods.

### *Supportive Nutrition for MCAS*

While the data regarding dietary interventions for mast cell disorders is scant, there is often an overlap with irritable bowel syndrome (IBS) symptomology (see "MCAS and IBS symptom overlap" below) and therefore similar dietary strategies may be used such as a trial of a low Fermentable Oligosaccharides, Disaccharides, Monosaccharides, and Polyols (FODMAP) diet (LFD).

In a study assessing self-perceived food triggers in IBS, 58% noted GI symptoms from histamine-releasing foods or foods rich in biogenic amines.[18] The role of histamine in the gut's immunoregulatory pathways has not been fully elucidated. Food-derived histamine is associated with non-allergic food intolerance and food poisoning (scombroid). Interestingly, McIntosh et al. found a LFD intervention reduced urinary histamine levels 8-fold.[19] This study suggests that a LFD intervention may play a role in reduction of histamine, a measure of immune activation. The LFD is a 3-phase diet intervention shown to effectively control digestive symptoms in about 50-70% of those with IBS.[20-22] It is plausible that endogenous histamine, in addition to exogenous histamine, may play a role in the pathomechanism of IBS as well as i-MCAS in some cases.

For diagnostic and symptom management purposes, a reduction in histamine-rich foods (Table 3) may be considered (if a patient exhibits an intolerance to high histamine foods as noted by food and symptom journaling and registered dietitian assessment). As with a LFD, a histamine elimination diet is not indicated long-term, but rather should be followed by a reintroduction phase to assess which foods are problematic and which are not.

**Table 1. Classic Symptoms of Mast Cell Activation Syndrome**

| SYMPTOMS |
|---|
| **Gastrointestinal** |
| • Abdominal pain and cramps |
| • Diarrhea |
| • Nausea +/- vomiting |
| • Abdominal bloating |
| **Skin** |
| • Flushing |
| • Hives/urticaria |
| • Pruritis |
| **Airway** |
| • Throat tightening sensation |
| • Rhinitis and sinus irritation |
| • Dyspnea and wheeze |
| **Neurological** |
| • Headache |
| • Brain fog |
| **Cardiovascular** |
| • Pre-syncope |
| • Palpitations |

***Note:*** *MCAS and Histamine Intolerance present with similar symptoms*

Controlled studies are needed to identity a potential biomarker for histamine intolerance, as well as an up to date analysis of histamine content of food and a benchmark for the upper limit of histamine in a food that would most likely elicit a pharmacologic effect.

A referral to a dietitian with knowledge in food intolerance is strongly recommended in patients with i-MCAS to support adequate nutrition and help minimize risk of over-restriction, escalation of food fears, or disordered eating. Dietitians with expertise in food intolerance can be found on the Academy of Nutrition and Dietetics website's section, Find an Expert (eatright.org/find-an-expert). Patients with

*(continued on page 30)*

(continued from page 28)

mast cell disorders often exhibit a level of food fear that may offer some innate protection, such as prompting avoidance of some foods to mitigate symptoms (authors' experience). However, this practice may be harmful and give rise to disordered or maladaptive eating. While not an overt eating disorder such as anorexia nervosa or bulimia, disordered eating (significant food restriction, skipping of meals, and fasting) may escalate food related anxiety and stress contributing to nutritional risk and possibly stress-induced mast cell activation. Dietary interventions should include screening for disordered eating or overt eating disorders such as anorexia nervosa or bulimia via tools such as the ARFID-9, to assess for Avoidant Restrictive Eating Disorder. The Eating Attitudes Test-26 (www.EAT-26.com) can be used to screen for an eating disorder, in an attempt to provide appropriate nutrition and psychological support for the patient's overall well being when indicated.[13,14]

Although formal studies are lacking, the optimal diet for MCAS may be one containing whole foods with reduction of ultra-processed foods and avoidance of perceived triggers and intolerances including dairy products high in lactose, wheat and gluten-containing foods, and food preservatives and dyes. In clinical observation, cases of highly symptomatic i-MCAS where patients are on a very limited diet, an elemental diet can be considered while medications are titrated to manage the mast cell activation. It is possible that an elemental diet or partially hydrolyzed formula (e.g. Absorb Plus®, Kate Farms®) offers benefit by reducing allergen load, minimizing FODMAP carbohydrates, modulating the gut microbiome, and/or potentially reducing mast cell activation. However, mechanistic studies are clearly needed to better understand the pathophysiology of diet in individuals with i-MCAS. Nutritional interventions in those with i-MCAS should be individualized to find what works best for the patient's total health.

## When is it Not MCAS?

### *MCAS and IBS Symptom Overlap*

Mast cells have many known physiologic functions in the GI tract, so it is not surprising that a condition where there is aberrant activation of mast cells may lead to multiple GI symptoms and manifestations. Furthermore, there have been many published studies to implicate mast cells in the symptoms of IBS. Patients with IBS have been found to have increased activation of mast cells in intestinal biopsies using various study methods compared to healthy controls.[15] The symptom of abdominal pain in IBS has been associated with activated mast cells, where higher amounts of histamine have been detected near nerve cells in the colon.[16] Endogenous histamine has also been linked as a mediator associated with the severity of symptoms in IBS.[17]

What differentiates i-MCAS from IBS is the presence of symptoms in more than one organ system. While several mast cell-specific medical therapies have been studied in IBS,[23,24] there are no convincing data to suggest that these therapies will work in the typical IBS patient who perhaps does not exhibit any allergy-type or mast cell symptoms.

### *What is Histamine Intolerance?*

Histamine intolerance (HI) is regarded as an imbalance of accumulated histamine and a reduced capacity for histamine degradation.[25] Within the GI tract, exogenous histamine levels can be impacted by:

- a reduction of diamine oxidase (DAO), the enzyme required to degrade dietary histamine
- consumption of a histamine rich diet
- and/or gut microbial metabolism of histidine, which may result in a potential histamine overload.

DAO is produced on the mature apical enterocytes on the upper intestinal villi. Gastroenteritis, small bowel inflammation, or a reduction in intestinal surface area may reduce production.[26] Symptoms associated with histamine intolerance mirror those of mast cell activation disorders including: headache, urticaria, hypotension, facial flushing, diarrhea, nausea, vomiting, vertigo, abdominal pain, congestion, rhinorrhea, and asthma (see Table 1).[17,25] Different than i-MCAS however, these symptoms are only experienced with eating.

The histamine content of foods can be variable depending on the microbial composition of the food product. Different microbes have varying capacities

**Table 2. Medication and Diet Interventions**[11,30,33,34]

| **First Line Medication Therapy**<br>*There are no FDA approved medications for MCAS* | **Practical Points** |
|---|---|
| **Histamine Blockers:**<br>$H_1$-antihistamines- fexofenadine (Allegra®), loratadine (Claritin®)<br>$H_2$-antihistamines- famotidine (Pepcid®), ranitidine (Zantac®) | Combination of H1 and H2 preferred and titrated to effect. Lowest dosage that treats symptoms should be continued for maintenance therapy (e.g. once daily dosing of each). Extra dose may be taken as needed on days with reactions. |
| **Mast Cell Stabilizers:**<br>Oral Cromolyn sodium | Standard maintenance dose for cromolyn: 200 mg 4x a day. Works best on empty stomach. Titrate slowly to this dose over 2-4 weeks. |
| Ketotifen | Standard dose ketotifen: 1mg capsule twice a day. Has to be compounded. Not FDA approved in oral form in U.S.A. |
| Leukotriene blockers (montelukast (Singulair®) | Standard maintenance dose: 10 mg at night. Caution if history of depression and black box warning for history of suicidality. |
| Prostaglandin blockers (aspirin) | Can be tried if documented elevations in PGD. Caution in first time users who may react to NSAIDs. Start at 81 mg a day and may titrate to as high as 325 mg bid. |
| Anti-IgE- omalizumab (Xolair®) | Recommend allergy/immunology referral. Used for more refractory cases and history of anaphylaxis. |
| **Diet Intervention**<br>*There are no evidenced based diet interventions for MCAS*<br>**Screen for disordered eating or eating disorder and consider referral to eating disorder specialist prior to recommending elimination diet.** | |
| **First Line Therapy:**<br>Encourage whole foods, minimize ultra-processed foods that are rich in preservatives, additives and alcohol. | Whole grains (gluten free options such as rice, quinoa, oats, more frequently), fresh meat, poultry, fish, fresh produce (except tomatoes, citrus and strawberries), milk and yogurt per tolerance, healthy fats (olive oil, nuts, seeds) |
| **Additional Diet Interventions that May be Helpful** | |
| If IBS symptoms are present, consider minimizing FODMAP intake or a full low FODMAP elimination diet as recommended by dietitian. | Two approaches to consider: reducing only the highest FODMAP containing foods in the diet or a full 3 phase low FODMAP elimination diet. |
| Consider histamine elimination and reintroduction diet, if patient notes histamine related food triggers along with MCAS symptoms. | Minimize histamine rich foods for 2-4 weeks to assess symptom benefit. This is followed by a reintroduction phase to identify particular food triggers and help liberalize diet. |
| In severe MCAS cases, where diet is felt to significantly impact symptom exacerbation, a trial of an elemental diet may be indicated. | Refer to dietitian to best guide this therapy to ensure patient acceptability to the product and that nutrient needs are being met. |

**Table 3. Foods Rich in Histamine**[30,35,36]

| General<br>• Consuming fresh, minimally processed foods over ultra-processed foods<br>• Freezing leftover protein rich foods to retard histamine production | |
|---|---|
| **Food types** | **High Histamine Foods** |
| **Fruit** | Avocado, citrus fruits, strawberries, kiwifruit, papayas, pineapples, dried fruits |
| **Vegetables** | Tomatoes, spinach, eggplant |
| **Animal Protein** | Fish: Mackerel, tuna, sardines, anchovies, herring, eggs<br>Aged beef, cured meats (salami, ham), leftover meats or fish |
| **Dairy** | Aged cheeses: Cheddar, Gouda, Roquefort, Parmesan |
| **Alcohol** | All, (Wine red > white) |
| **Other** | Nuts, chocolate, vinegar, fermented foods such as kimchi, sauerkraut |

to produce histamine; how the product is stored and prepared can also influence microbial growth.[27] Fresh foods tend to be lower in histamine than the preserved, cured, or fermented counterparts. Alcohol has variable histamine levels with red wine generally yielding higher amounts compared to beer. Interestingly, many alcoholic beverages contain histamine and additionally suppress DAO production, potential resulting in a dual pathway for abnormal histamine regulation.[28] Concurrent prevalence of low DAO activity and carbohydrate malabsorption was assessed in a recent retrospective analysis in individuals presenting with GI symptoms revealing that more than one-third of those diagnosed with carbohydrate malabsorption experienced HI. Individuals were considered positive for HI if they presented with a low DAO activity (< 10 mU/ml serum DAO) and symptoms such as nausea, bloating, and pain. In addition to its retrospective nature, this study has other limitations as the diagnosis of HI lacks standardized testing or definitive biomarkers.[29] Plasma DAO and blood histamine levels are not always reproducible in the clinic setting.[26] Presently, the diagnosis of HI is based on the following criteria[30]:

- presentation of two or more histamine intolerance symptoms,
- improvement with a low histamine diet
- improvement with antihistamine medications.

Some general recommendations to reduce dietary histamine include reducing high histamine foods, freezing leftover protein rich foods to retard histamine production, and consuming fresh, minimally processed foods over ultra-processed foods (Table 3).

## Other GI-Specific Diseases that are Not MCAS

An important part of the proposed diagnostic criteria for i-MCAS is that no other condition better explains the symptoms and manifestations of the patient. In those with prominent GI symptoms, appropriate tests should be undertaken to rule out inflammatory conditions (e.g. inflammatory bowel diseases, celiac disease, eosinophilic disorders), GI tract malignancies, or anatomic defects. Small intestinal bacterial overgrowth.[31] may mimic symptoms of mast cell activation or be found concurrently in patients with MCAS. Although there is no published data, patients with MCAS report frequent exposure to antibiotics and may therefore have at least an intestinal dysbiosis. Bile salt diarrhea is also possible, especially in those patients who have had cholecystectomies and/or other abdominal surgeries in previous efforts to address patients' symptoms.[32] GI motility disturbances due to autonomic dysfunction should also be ruled out due to the overlap in patients with MCAS and dysautonomia. Bear in mind that MCAS patients can have more than one diagnosis.

## Other Systemic Conditions that are Not MCAS

There is often a substantial delay in the diagnosis of i-MCAS and patients may experience symptoms for many years and undergo many tests and specialty

consultations resulting in multiple diagnoses. Chronic symptom disorders that may be confused with i-MCAS include chronic pain syndromes, chronic fatigue syndrome, fibromyalgia, multiple chemical sensitivity syndrome, and chronic symptom syndromes following infections or other exposures such as the chronic Lyme disease syndrome. Various auto-immune diseases, endocrinopathies, and psychiatric conditions should also be in the differential for i-MCAS, and if present, may better explain the patient's presentation.

## Summary Statements

The incidence and prevalence of i-MCAS may be increasing in many societies perhaps in parallel with other allergic and atopic conditions. With a current paucity of diagnostic biomarkers and robust clinical and scientific literature to support the pathology of mast cell activation in patients with the multi-symptom disorder, there is a lack of provider awareness of i-MCAS. Furthermore, the lay literature on the Internet, social media "experts", and patient blogs are outpacing the science. We therefore have to remain faithful to the proposed diagnostic criteria for patients with suspected i-MCAS and continue to expand our research to be able to develop more objective biomarkers. Patients with i-MCAS do exist in your practice and we have outlined clinical management approaches that will undoubtedly help them. ■

## References

1. Akin C, Valent P, Metcalfe DD. Mast cell activation syndrome: Proposed diagnostic criteria. J Allergy Clin Immunol 2010;126 (6):1099-1104.e4.
2. Akin C. Mast cell activation syndromes. J Allergy Clin Immunol 2017;140(2):349-355.
3. Valent P, Escribano L, Broesby-Olsen S, et al. Proposed diagnostic algorithm for patients with suspected mastocytosis: a proposal of the European Competence Network on Mastocytosis. Allergy 2014;69 (10):1267-1274.
4. Doyle LA, Sepehr GJ, Hamilton MJ, et al. A clinicopathologic study of 24 cases of systemic mastocytosis involving the gastrointestinal tract and assessment of mucosal mast cell density in irritable bowel syndrome and asymptomatic patients. Am J Surg Pathol 2014;38(6):832-843.
5. Valent P, Akin C, Arock M, et al. Definitions, criteria and global classifications of mast cell disorders with special reference to mast cell activation syndromes: a consensus proposal. Int Arch Allergy Immunol 2012;157(3);215-225.
6. Akin C. Mast cell activation syndromes presenting as anaphylaxis. Immunol Allergy Clin North Am 2015; 35(2):277-285.
7. Kohn A, Chang C. The Relationship Between Hypermobility Ehlers-Danlos Syndrome (hEDS), Postural Orthostatic Tachycardia Syndrome (POTS) and Mast Cell Activation Syndrome (MCAS). Clin Rev Allergy Immunol 2019 epub ahead of print. https://doi.org/10.1007/s12016-019-08755-8
8. Shibao C, Arzubiaga C, Roberts LJ, et al. Hyperadrenergic postural tachycardia syndrome in mast cell activation disorders. Hypertension 2005;45(3):385-390.
9. Lyons JJ. Hereditary alpha tryptasemia: genotyping and associated clinical features. Immunol Allergy Clin North AM 2018;38(3):483-495.
10. Weiler CR, Austin KF, Akin C, et al. AAAAI mast cell disorders committee work group report: mast cell activation syndrome diagnosis and management. J Allergy Clin Immunol 2019;144(4):883-895
11. Jennings S, Russell N, Jennings B. et al. The Mastocytosis Society Survey on Mast Cell Disorders: Patient Experiences and Perceptions. J Allergy Clin Immunol Pract 2014;2(1):70-6.
12. Hamilton MJ, Hornick JL, Akin C, et al. Mast cell activation syndrome: a newly recognized disorder with systemic clinical manifestations. J Allergy Clin Immunol 2011;128(1):147-152
13. Zickgraf HF, Ellis JM. Initial validation of the Nine Item Avoidant/Restrictive Food Intake disorder screen (NIAS): A measure of the three restrictive eating patterns. Appetite 2018; 123:32-42.
14. Eating attitudes test (EAT-26). 2009-2017. www.EAT-26.com
15. Boeckxstaens GE. Gastroenterol Hepatol (N Y) 2018 Apr; 14(4): 250–252.
16. Barbara G, Stanghellini V, De Giorgio R, et al. Activated mast cells in proximity to colonic nerves correlate with abdominal pain in irritable bowel syndrome. Gastroenterology 2004;126:693–702.
17. Smolinska S, Jutel M, Crameri R, et al. Histamine and gut mucosal immune regulation. Allergy 2014;69(3):273-281.
18. Bohn L, Storsrud S, Tornblom H, et al. Self-reported food-related gastrointestinal symptoms in IBS are common and associated with more severe symptoms and reduced quality of life. Am J Gastroenterol. 2013;(108):634-641.
19. McIntosh K, Reed DE, Schneider T, et al. FODMAPs alter symptoms and the metabolome of patients with IBS: a randomized controlled trial. Gut 2017;66(7):1241-1251.
20. Halmos EP, Power VA, Shepherd SJ, et al. A diet low in FODMAPs reduces symptoms in irritable bowel syndrome. Gastroenterology 2014:146(1):67-75.
21. Eswaran SL, Chey WD, Han-Markey T, et al. A Randomized Controlled Trial Comparing the Low FODMAP Diet vs Modified NICE Guidelines in US Adults with IBS-D. Am J Gastroenterol 2016;111(12):1824-1832.
22. Barrett JS. How to institute the low-FODMAP diet. J Gastroenterol Hepatol. 2017;32 Suppl 1:8-10.
23. Klooker TK, Braak B, Koopman KE, et al. The mast cell stabilizer ketotifen decreases visceral hypersensitivity and improves intestinal symptoms in patients with irritable bowel syndrome. Gut 2010;59(9):1213-1221
24. Lobo B, Ramos L, Martinez C, et al. Downregulation of mucosal mast cell activation and immune response in diarrhea-irritable bowel syndrome by oral disodium cromoglycate: a pilot study. United European Gastroenterol J 2017;5(6):887-897.
25. Maintz L, Novak J. Histamine and histamine intolerance. Am J Clin Nutr. 2007;85(5):1185-1196.
26. Rosell-Camps A, Zobetto S, Perez-Esteban G, et al. Histamine Intolerance as a cause of chronic digestive complaints in pediatric patients. Rev Esp Enferm Dig 2013;105(4):201-207.
27. Doeun D, Davaatseren M, Chung MS. Biogenic amines in foods. Food Sci Biotechnol. 2017;26(6):1463–1474.
28. Wantke F, Gotz M, Jarisch R. The red wine provocation test: intolerance to histamine as a model for food intolerance. Allergy Proc 1994;15(1):27-32.
29. Enko D, Meinitzer A, Mangge H, et al. Concomitant Prevalence of Low Serum Diamine Oxidase Activity and Carbohydrate Malabsorption. Canadian J Gastro Hepatol 2016;2016:4893501.
30. Tuck Caroline J, Biesiekierski JR, Schmid-Grendelmeier, et al. Food Intolerances. Nutrients 2019;11:1684.
31. Quigley EMM. The spectrum of small intestinal bacterial overgrowth. Curr Gastro Rep 2019;21(1):3
32. Vijayvargiya P, Camilleri M. Update on bile acid malabsorption: finally ready for prime time?. Curr Gastroenterol Rep. 2018;26(3):10
33. Hamilton MJ. Nonclonal Mast Cell Activation Syndrome A Growing Body of Evidence Immunol Allergy Clin N Am 2018;38;469-481.
34. Molderings GJ, Haenisch B, Brettner S, et al. Pharmacological treatment options for mast cell activation disease. Naunyn Schmiedebergs Arch Pharmacol. 2016;389(7):671–694.
35. Spencer M, Chey WD, Eswaran S. Dietary Renaissance in IBS: Has Food Replaced Medications as a Primary Treatment Strategy? Curr Treat Op Gastroenterol. 2014;12:424-440.
36. Sánchez-Pérez S, Comas-Basté O, Rabell-González J, et al. Biogenic Amines in Plant-Origin Foods: Are They Frequently Underestimated in Low-Histamine Diets?. Foods. 2018;7(12):205.