

## Review Article

# Mast Cell Activation Disease and Microbiotic Interactions

Lawrence B. Afrin, MD<sup>1</sup>; and Alexander Khoruts<sup>2</sup>

<sup>1</sup>*Division of Hematology, Oncology, and Transplantation, University of Minnesota, Minneapolis, Minnesota; and* <sup>2</sup>*Division of Gastroenterology and Center for Immunology, BioTechnology Institute, University of Minnesota, Minneapolis, Minnesota*

### ABSTRACT

**Purpose:** This article reviews the diagnostically challenging presentation of mast cell activation disease (MCAD) and current thoughts regarding interactions between microbiota and MCs.

**Methods:** A search for all studies on interactions between mast cells, mast cell activation disease, and microbiota published on [pubmed.gov](http://pubmed.gov) and [scholar.google.com](http://scholar.google.com) between 1960 and 2015 was conducted using the search terms mast cell, mastocyte, mastocytosis, mast cell activation, mast cell activation disease, mast cell activation syndrome, microbiome, microbiota. A manual review of the references from identified studies was also conducted. Studies were excluded if they were not accessible electronically or by interlibrary loan.

**Findings:** Research increasingly is revealing essential involvement of MCs in normal human biology and in human disease. Via many methods, normal MCs—present sparsely in every tissue—sense their environment and reactively exert influences that, directly and indirectly, locally and remotely, improve health. The dysfunctional MCs of the “iceberg” of MCAD, on the other hand, sense abnormally, react abnormally, activate constitutively, and sometimes (in mastocytosis, the “tip” of the MCAD iceberg) even proliferate neoplastically. MCAD causes chronic multisystem illness generally, but not necessarily, of an inflammatory  $\pm$  allergic theme and with great variability in behavior among patients and within any patient over time. Furthermore, the range of signals to which MCs respond and react include signals from

the body’s microbiota, and regardless of whether an MCAD patient has clonal mastocytosis or the bulk of the iceberg now known as *MC activation syndrome* (also suspected to be clonal but without significant MC proliferation), dysfunctional MCs interact as dysfunctionally with those microbiota as they interact with other human tissues, potentially leading to many adverse consequences.

**Implications:** Interactions between microbiota and MCs are complex at baseline. The potential for both pathology and benefit may be amplified when compositionally variant microbiota interact with aberrant MCs in various types of MCAD. More research is needed to better understand and leverage these interactions. (*Clin Ther.* 2015;37:941–953) © 2015 Elsevier HS Journals, Inc. All rights reserved.

**Key words:** mast cell, mast cell activation disease, mast cell activation syndrome, mastocytosis, microbiota.

### INTRODUCTION

First identified in 1863, mast cells (MCs, from the German *mastzellen*, or “well-nourished cells,” from rich granular content seen on metachromatic staining) soon were associated with disease in the rare neoplastic skin malady urticaria pigmentosa and then a half-century later with even rarer internal neoplasia, now called *systemic mastocytosis* (SM).<sup>1</sup> MCs crucially effect and regulate adaptive and innate immunity. The identification of variably expressed signaling molecules, or “mediators,” in MCs began in 1937 with heparin. More than 200 MC

Accepted for publication February 3, 2015.  
<http://dx.doi.org/10.1016/j.clinthera.2015.02.008>  
 0149-2918/\$ - see front matter

© 2015 Elsevier HS Journals, Inc. All rights reserved.



Scan the QR Code with your phone to obtain FREE ACCESS to the articles featured in the Clinical Therapeutics topical updates or text GS2C65 to 64842. To scan QR Codes your phone must have a QR Code reader installed.

mediators are known (although few specific to MCs), including tryptase, histamine, and certain prostaglandins and leukotrienes.<sup>2</sup> MCs secrete prestored mediators and synthesize mediators in response to allergic, microbial, and nonimmune triggers. Widely, sparsely distributed, and of hematopoietic origin, MCs essentially contribute to many processes, including defense, growth, and healing. Among the oldest host defense cells, putatively arising in multicellular eukaryotes some 500 million years ago,<sup>3</sup> MCs possess large arrays of potent sensory and response mechanisms, with tissue-specific sensitivities activating numerous intracellular pathways intersecting to modulate the quality and magnitude of response. Best characterized among MC activation mechanisms is antigenic cross-linking of immunoglobulin (Ig) E bound to MC-surface high-affinity IgE receptor (FcεRI). MCs also express G-protein-coupled receptors and other IgE-independent recognition sites. Basic insights into MC biology continue emerging, including the recent recognition that serum tryptase reflects more the body's MC load than activation state.<sup>1</sup>

Apart from the involvement in allergy, MCs leverage mediators to crucially assist in maintaining integrity and function in all tissues.<sup>2</sup> MCs regulate defense by acting as innate immune cells, by interacting with the specific immune system, and by inducing and regulating inflammation.<sup>2</sup> MCs orchestrate microbial, toxic, and physical environmental defenses and recruit other immune cells to injury sites.<sup>2</sup> MCs regulate homeostasis, too, contributing crucially to tissue remodeling, including wound healing.<sup>2</sup> MCs promote homeostasis by degrading endogenous and bacterial toxins.<sup>2</sup> MCs release mediators via classic degranulation, selective secretion ("piecemeal" or "differential" degranulation), and transgranulation.<sup>4,5</sup> Evolutionary success of these mechanisms is due to fine regulation, inferring potential for multisystem havoc from dysregulated MCs.

Classic thought attributed much of allergy to aberrant MC reactivity, while constitutive activation drove MC neoplasia (cutaneous mastocytosis [CM], SM, and rare solid MC tumors). We now understand that frankly malignant MC proliferation drives stark MC accumulation in aggressive forms of mastocytosis, whereas anti-apoptosis drives modest accumulations seen in more common, indolent forms of mastocytosis.<sup>1</sup> Speculation about MC disease featuring constitutive activation without neoplasia emerged in 1991<sup>6</sup>; case reports were first published in 2007.<sup>7,8</sup> Crucial insight into the marked

clinical heterogeneity of relatively nonproliferative MC activation syndrome (MCAS) came with the discovery of many mutations in MC Kit mRNA in a cohort of patients with MCAS (findings later extended including healthy controls largely absent such mutations).<sup>9,10</sup> Multiple investigators soon reported that most mastocytosis cases, too, harbor multiple mutations across many MC regulatory genes, epigenes, and microRNAs.<sup>1</sup>

Expressed 10-fold brighter in MCs than any other human cells, transmembrane tyrosine kinase KIT is the dominant MC regulator.<sup>2</sup> Binding of stem cell factor to homodimeric KIT conformationally changes the intracellular domains of KIT, effecting autoinhibition at the juxtamembrane domain and activation of kinase domains, consequently promoting MC survival, mediator production and release, and other functions. Thus, varied constitutively activating mutational patterns in MC KIT would be expected to produce varied clinical presentations. KIT<sup>D816V</sup> is consistently found in SM (>90% of cases)<sup>2</sup> and likely drives prominent pathologic features, including MC proliferation, aggregation, spindling, tryptase over-expression, and CD25 coexpression.<sup>2</sup> However, repeated findings that patients with MCAS harbor multiple mutations in KIT, albeit in no yet-apparent recurrent patterns<sup>9,10</sup> (and almost never including KIT<sup>D816V</sup>), together with similar mutational heterogeneity in KIT and other MC regulatory elements in patients with mastocytosis,<sup>11</sup> align with observations of marked clinical heterogeneity in patients with MCAS and mastocytosis. Although MCAS appears usually clonal in the research laboratory, most commercial laboratories today assess MC clonality only by KIT mutation analysis at codon 816 (via polymerase chain reaction) or by MC CD25 or CD2 expression (by flow cytometry). As these signatures appear rare in MCAS, diagnosis presently rests on finding elevated MC mediator levels and excluding differential diagnoses.

Like most neoplasms, mastocytosis usually stems from somatic mutations; germ line mutations are rare.<sup>11</sup> MCAS appears similar.<sup>11,12</sup> Yet, a familial predisposition for MC activation disease (MCAD) has been demonstrated.<sup>11,13</sup> Complexity multiplies on recognition that different affected members of an affected kindred usually bear disparate presentations and MC mutational profiles. Perhaps inheritable epigenetic mutations create genetic fragility states susceptible to specific stressors, inducing specific (and/or random?) stem cell or progenitor mutations principally operant in

MCs. Evidence for epigenetic pathogenicity in MCAD is emerging; patients with MCAD bear abnormal epigenomes.<sup>11,12,14</sup> However, lifestyle-influenced factors, such as diet; alcohol use; and, yes, microbiota,<sup>15,16</sup> may influence MCAD phenotype.

In 2010, the recognition that all MC disease manifests aberrant MC activation engendered new top-level designation of MCAD encompassing all pathologic MC states.<sup>1</sup> Rare, proliferative CM and SM compose one element of MCAD, while forms of (relatively nonproliferative) MCAS compose other elements of MCAD. Except in aggressive mastocytoses, the distinctions between MCAS and mastocytosis are principally pathologic (eg, significantly elevated serum tryptase and gross MC proliferation present in mastocytosis but absent in MCAS) and appear clinically inconsequential. Two proposals, of varying strengths, for MCAS diagnostic criteria have emerged (Figure 1).<sup>17</sup> The diagnosis and treatment of MCAD are complex; interested readers should consult recent reviews.<sup>1,2,17</sup>

Truly reactive/secondary MCAS is increasingly difficult to identify given rising recognition that diseases previously thought to provoke MC activation may actually be sparked by primary MCAS. It seems likely that given presentations of mastocytosis and primary MCAS result from specific mutation sets driving specific patterns of aberrant constitutive MC activation as well as aberrant MC reactivity, the effects of which may be direct and/or indirect as well as local and/or remote, ultimately affecting normal cells, other abnormal MCs, and other abnormal cells potentially harboring similar mutations. Effects in these other cells may “rebound,” too, to further activate the instigating abnormal MCs. Presently, commercial probing for MC mutations is very limited (essentially only KIT<sup>D816V</sup>). Although some subclassify MCAS as primary (clonal), secondary (reactive), and idiopathic<sup>1</sup> (or nonclonal<sup>18</sup>), perhaps subclassification as clonal and undetermined clonality is more accurate. When readily commercially available, whole genome/exome sequencing of isolated MCs may prove instructive.

Thus, after 150 years of orthodoxy that MC disease is principally allergic phenomena and neoplastic mastocytosis, it is now evident that such entities merely “cap” an MCAD “iceberg” (Figure 2), with non-neoplastic MCAS composing the largely unrecognized bulk of MCAD for reasons reviewed subsequently.

As recognition of MCAD/MCAS has expanded, so, too, has recognition of the importance of human

microbiota to health and disease, including crucial interactions with MCs. Below we review highlights of MCAD and current thoughts regarding microbiotic interactions with MCs and MCAD.

## MATERIALS AND METHODS

A search for all studies on interactions between mast cells, mast cell activation disease, and microbiota published on [pubmed.gov](http://pubmed.gov) or [scholar.google.com](http://scholar.google.com) between 1960 and 2015 was conducted using the search terms mast cell, mastocyte, mastocytosis, mast cell activation, mast cell activation disease, mast cell activation syndrome, microbiome, microbiota. A manual review of the references from identified studies was also conducted. Studies were excluded if they were not accessible electronically or by interlibrary loan.

## RESULTS

A total of 140 studies were identified and included in the present review. Studies not specifically cited were excluded due to redundancy of results and citation limits.

### Mast Cell Activation Disease *Epidemiology, Natural History, Prognosis, and Familial Considerations*

Mastocytosis is rare. The estimated incidence in western Europe is 5 to 10 per 1 million population per year<sup>19,20</sup>; the prevalence is 0.3 to 13 to 100,000.<sup>11</sup> Only preliminary epidemiologic data on MCAS have been reported. In Germany, the prevalence of MCAD has been estimated at 5% to 10% of the general population,<sup>11–13</sup> which may be unsurprising because MCAS may underlie many common conditions in subsets of patients, such as those with fibromyalgia and irritable bowel syndrome (IBS).<sup>2</sup> CM cases outnumber SM by 10 to 1.<sup>12</sup> Most CM presents in childhood, commonly spontaneously regressing by late adolescence, but later emergence of possibly MCAS-attributable illnesses calls into question whether spontaneous cure truly occurs.

Mastocytosis occurs equally in males and females<sup>21</sup>; in MCAS, females seemingly prevail by 3 to 1,<sup>12</sup> but given only recent recognition of MCAS and the erratic, nebulous, generally non-life-threatening symptoms of MCAD, affected males may underpresent. No racial predilection is known.

SM typically emerges in middle age or later. In MCAS, symptoms typically first manifest in adolescence or earlier. Most MCAD symptoms are nonspecific,

## WHO 2008 Diagnostic Criteria for Systemic Mastocytosis

## Major Criterion:

1. Multifocal, dense aggregates of MCs (15 or more) in sections of bone marrow or other extracutaneous tissues and confirmed by tryptase immunohistochemistry or other special stains

## Minor Criteria:

1. Atypical or spindled appearance of at least 25% of the MCs in the diagnostic biopsy
2. Expression of CD2 and/or CD25 by MCs in marrow, blood, or extracutaneous organs
3. KIT codon 816 mutation in marrow, blood, or extracutaneous organs
4. Persistent elevation of serum total tryptase > 20 ng/ml

Diagnosis of SM made by either (1) major criterion + any one or more minor criteria, or (2) any three minor criteria.

## Proposed Diagnostic Criteria for Mast Cell Activation Syndrome

## Valent et al. Criteria

1. Chronic/recurrent symptoms (flushing, pruritus, urticaria, angioedema, nasal congestion or pruritus, wheezing, throat swelling, headache, hypotension, and/or diarrhea) consistent with aberrant MC mediator release
2. Absence of any other known disorder that can better account for these symptoms
3. Increase in serum total tryptase of [20% above baseline, plus another 2 ng/ml] during, or within 4 hours after, a symptomatic period
4. Response of symptoms to histamine H<sub>1</sub> and/or H<sub>2</sub> receptor antagonists or other "MC-targeting" agents such as cromolyn.

## Molderings et al. Criteria

## Major Criteria:

1. Multifocal MC aggregates as per WHO major criterion for SM
2. Clinical history consistent with chronic/recurrent aberrant MC mediator release

## Minor Criteria:

1. Abnormal MC morphology as per WHO SM minor criterion #1
2. CD2 and/or CD25 expression as per WHO SM minor criterion #2
3. Detection of known constitutively activating mutations in MCs in blood, marrow, or extracutaneous organs
4. Elevation in serum tryptase or chromogranin A, plasma heparin or histamine, urinary N-methylhistamine, and/or other MC-specific mediators such as (but not limited to) relevant leukotrienes (B<sub>4</sub>, C<sub>4</sub>, D<sub>4</sub>, E<sub>4</sub>) or PGD<sub>2</sub> or its metabolite 11-β-PGF<sub>2α</sub>.

Diagnosis of MCAS made by either (1) both major criteria, or (2) the second major criterion plus any one of the minor criteria, or (3) any three minor criteria.

Figure 1. Diagnostic criteria for systemic mastocytosis (SM) and mast cell activation syndrome (MCAS).<sup>17</sup>  
PG = prostaglandin; WHO = World Health Organization.

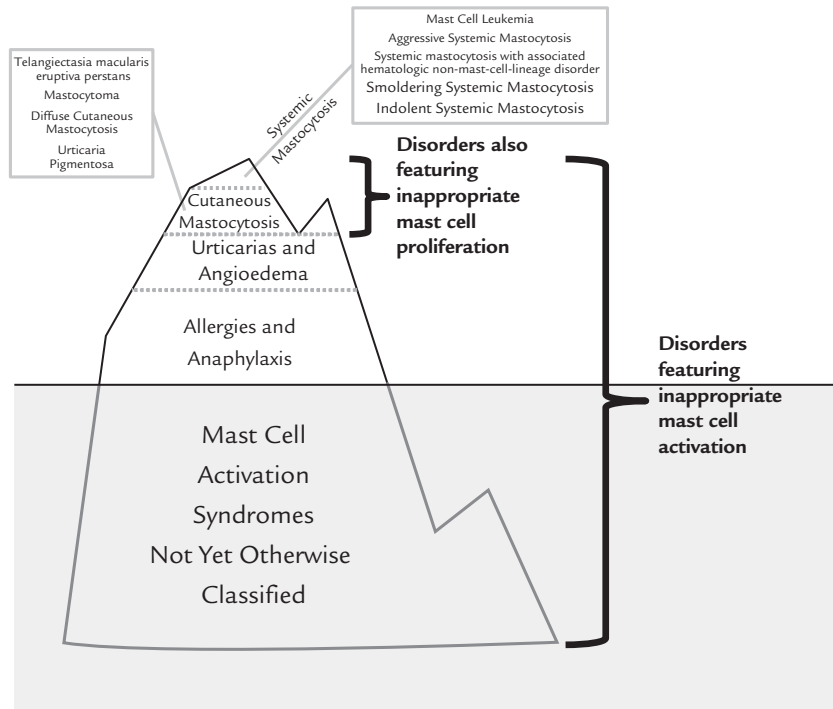


Figure 2. An iceberg-type metaphoric conception of the spectrum of disorders of mast cell (MC) activation, with typically vividly presenting entities arrayed above a “waterline” of relatively easy clinical recognizability in order of estimated prevalence.<sup>1</sup> The most recently recognized entity, MC activation syndrome (MCAS), with recent preliminary prevalence estimates of 5% to 10%, may be “hidden below the waterline,” or more difficult to clinically recognize, due to heterogeneity of presentation, fewer visually distinctive signs, and other factors. The various forms of mastocytosis are mutationally rooted, primary MC diseases, as are rare variants of MCAS which can be proven monoclonal (although clinical laboratory testing for such at present is largely constrained to [1] probing by polymerase chain reaction for the constitutively activating *KIT*<sup>D816V</sup> mutation, and [2] testing by flow cytometry for MCs bearing pathognomonically aberrant CD117<sup>+</sup>CD25<sup>+</sup> or CD117<sup>+</sup>CD2<sup>+</sup> signatures, which, when present, often compose very small portions (<1%) of the tested cell population). Other classic MC-activation disorders have long been thought to be secondary/reactive MC diseases, although more extensive mutational analyses have suggested recently that most MCAS cases, like mastocytosis, are also mutationally rooted.

recognized only in retrospect as MCAD related; careful history often finds decades of latency between symptom onset and diagnosis in SM and MCAS.<sup>1,2,22,23</sup>

MCAD naturally features periods of relatively stable symptoms (waxing and waning somewhat but also occasionally with unpredictable, potentially severe acute flares), punctuated by often permanent stepwise escalations in baseline symptom profiles soon after major stressors both predictably physiologic (eg, puberty) and unpredictably pathologic (eg, physical/psychological trauma, infection). Such escalations

possibly reflect subclonal evolution. Eventually, paucisymptomatic periods shorten and chronic symptoms intensify. Careful history taking in patients with MCAD usually shows that patients rarely are truly symptom-free and commonly identifies a major stressor or novel exposure shortly antedating a general decline in health leading to presentation. Such patients sometimes are convinced that the stressor/exposure caused the illness, but careful history usually reveals MCAD-attributable symptoms present long before the “turning point.”



Expected life span is normal with indolent SM (~90% of SM).<sup>21,24,25</sup> Advanced mastocytosis (SM with eosinophilia or associated hematologic malignancy, aggressive SM, and MC leukemia) confers worse survival (as short as 6 months with MC leukemia),<sup>21,23,24</sup> although investigational therapies appear promising. Aggressive SM features, so-called “B- and C-findings,” reflect larger MC loads, expansion of genetic defects into other myeloid lineages, and impaired organ function due to MC infiltration.<sup>21,23,24,26</sup> Transformation of indolent SM to advanced types appears rare<sup>27</sup>; MCAS has not been so studied, but the authors have never observed MCAS transform to mastocytosis. Although no formal survival studies have been reported, MCAS appears to course similarly to indolent SM, that is, life of normal span, if morbid until the disease is diagnosed and effectively controlled.

Most MCAD-associated mutations appear somatic,<sup>12</sup> but familial MCAD appears common and may be an epigenetic phenomenon.<sup>13,14</sup> Approximately 75% of index patients with MCAD have at least 1 afflicted first-degree relative,<sup>13</sup> suggesting substantial inheritability. Approximately half of patients with MCAD have children who also appear afflicted to varying degrees,<sup>13</sup> but without predictors of risk for MCAD, no recommendations can be given regarding reproductive decisions.

### Clinical Presentation

MCAD presents diversely (Table; more detail presented by Afrin<sup>2</sup>) due to widespread MC distribution and great heterogeneity of aberrant mediator expression patterns, potentiating many anomalies in any or all tissues. The nonspecific nature of almost every symptom often foils clinical recognition until decades later, if ever.<sup>1</sup> Symptoms often are “inflammatory”; arise acutely, subacutely, or chronically/developmentally; persist, waxing and waning to varying degrees at unpredictable times; and sometimes remit and then (again, unpredictably) relapse. Given their common absence of histologically detectable MC neoplasia, patients with MCAS often seem inexplicably, chronically, and multisystemically ill, perhaps recognized as having an inflammatory disease but one that does not “fit” any well-known such syndrome. No system is spared potential impact, but there is no certainty that any given system will be affected. Disability is common, sometimes severe.

“Routine” diagnostics often yield normal or equivocal results, or mild to moderate, but ephemeral, abnormalities. Presenting symptoms usually are subtle to moderate but may be severe or even life-threatening (eg, non-atherosclerotic myocardial infarction [often unrecognized as the vasospastic allergic angina of Kounis syndrome], end-stage renal failure, refractory diarrhea), leading to “exhaustive,” nondiagnostic testing, whereupon psychosomatism is commonly misdiagnosed (especially if presentation includes classic neuropsychiatric symptoms).<sup>1,2</sup> Reflecting mutational heterogeneity, MCAD can present opposite abnormalities in different patients (eg, diarrhea vs constipation, polycythemia vs anemia) or in a given patient at different times (eg, alternating diarrhea and constipation) or simultaneously (eg, coexisting osteoporosis and osteosclerosis).<sup>1,2</sup> Acute “flares” or “spells” are common, often occasioning urgent evaluations that, although necessary to rule out other illnesses, frequently are unrevealing, heightening suspicions of psychosomatism. Commonly, many idiopathic diagnoses accrue (and respond poorly to treatment) (eg, fibromyalgia, chronic fatigue, neurogenic pain, IBS, hypermobility-type Ehlers-Danlos syndrome, postural orthostatic tachycardia, histamine intolerance, dysautonomia, anxiety/panic, interstitial cystitis [itself often misdiagnosed as culture-negative urinary tract infection]). Some yet-undiagnosed patients with MCAD have definitive comorbidities (eg, sickle cell anemia or obesity) blamed for many symptoms despite difficulty of attribution, by known (patho)biological pathways, of such symptoms to such ailments.<sup>1,2</sup>

Aberrant reactivities may be prolific, odd, and, when medication related, directed against excipients, not active ingredients. Some “allergies” (eg, to iodine or even water!) may seem psychosomatic until the recognition of excipient (eg, povidone in iodine/povidone solution) or physical (eg, temperature) triggers.

Complete history taking helps to establish suspicion for MCAD. History must include a thorough systems review, as many patients with MCAD have ailed for so long that they accept much of their illness as “normal,” or they tire or become wary, after so many nondiagnostic evaluations or suspicions of psychosomatism, of reporting certain symptoms.

### Interactions between Human Microbiota and Mast Cells

The gut has dominated research on microbiota. Gut microbiota are now recognized as a “microbial organ,”

Table. Symptoms and findings in mast cell (MC) activation disease.<sup>\*,2,22,23</sup>

System	Potential Manifestations of Mast Cell Disease
Constitutional	Fatigue, malaise, asthenia, chronic fatigue syndrome, subjective and/or objective hyperthermia and/or hypothermia, sense of “feeling cold much of the time,” sweats/diaphoresis (not always nocturnal), flushing, plethora or pallor, increased or decreased appetite, early satiety, weight gain or loss, pruritus, environmental sensitivities (often odd)
Dermatologic	Rashes and lesions of many sorts (classic urticaria pigmentosa, “freckles,” telangiectatic/angiomatic lesions, xerosis, warts, tags, folliculitis, ulcers, diffusely migratory but sometimes focally persistent patchy erythema), pruritus (often diffusely migratory, sometimes aquagenic), flushing, angioedema, striae, dermatographism, poor healing
Ophthalmologic	Irritated eyes, increased or decreased lacrimation, suffusion, conjunctivitis, difficulty focusing, lid tremor/tic, solar sensitivity, infectious or sterile inflammation
Otologic	Infectious or sterile otitis externa and/or media, hearing loss or hyperacusis, tinnitus, otosclerosis
Oral/oropharyngeal	Pain (sometimes “burning”), leukoplakia, fibrosis, lichen planus, ulcers, sores, angioedema, dental decay, dysgeusia, throat tickle/discomfort/irritation/pain, postnasal drip
Lymphatic	Adenopathy, usually sub-pathologic and often waxing/waning in size, sometimes asymptomatic but not uncommonly tender, sometimes focal, sometimes migratory, pathology usually shows a reactive lymphocytosis or sometimes an atypical non-specific lymphoproliferative disorder; left upper quadrant discomfort (likely from release of mediators from splenic MCs with or without detectable splenomegaly)
Pulmonary	Rhinitis, sinusitis, pharyngitis, laryngitis, bronchitis, pneumonitis (often confused with infectious pneumonia), cough, dyspnea (often low-grade, inconstant, “I just can't catch a deep breath” despite normal pulmonary function tests), wheezing, obstructive sleep apnea, pulmonary hypertension
Cardiovascular	Presyncope (lightheadedness, weakness, dizziness, vertigo) and/or syncope, hypertension and/or hypotension, palpitations, dysrhythmias, chest discomfort or pain (usually non-anginal in character), coronary and peripheral arterial atherosclerosis/spasm/infarction, aneurysms, hemorrhoids, varicosities, aberrant angiogenesis (hemangiomas, arteriovenous malformations, telangiectasias), migratory edema (often non-dependent and in spite of normal cardiac and renal function)
Gastrointestinal	Aerophagia, angioedema in any segment of the luminal tract, dysphagia (often proximal, possibly due to pharyngeal angioedema), pain/inflammation (often migratory) in one or more segments of the luminal tract (from esophagitis to proctitis) and/or one or more solid organs (eg, hepatitis, pancreatitis), queasiness, nausea, vomiting, diarrhea and/or constipation (often alternating), malabsorption (more often selective micronutrient malabsorption than general protein-calorie malabsorption), ascites either from portal hypertension and/or peritoneal serositis; gastroesophageal reflux disease (often “treatment refractory”) and inflammatory/irritable bowel syndrome are common preexisting diagnoses
Genitourinary	Inflammation (often migratory) in one or more segments of the luminal tracts (ureteritis, cystitis, urethritis, vaginitis, vestibulitis) and/or one or more solid organs

(continued)

Table. (continued).

System	Potential Manifestations of Mast Cell Disease
	(eg, nephritis, prostatitis), chronic kidney disease, endometriosis, chronic low back pain or flank pain or abdominal pain, hydronephrosis (likely from ureteral angioedema), infertility, erectile dysfunction, decreased libido; in the appropriate setting of multisystem morbidity, miscarriages should prompt consideration of antiphospholipid antibody syndrome potentially due to MCAS
Musculoskeletal	Clinical myositis, often diffusely migratory (fibromyalgia is a common pre-existing diagnosis), subclinical myositis (i.e., asymptomatic elevated creatine kinase not otherwise explained), arthritis (typically migratory), joint laxity/hypermobility, osteoporosis/osteopenia, osteosclerosis, sometimes mixed osteoporosis/osteopenia/osteosclerosis; MCAS-driven musculoskeletal pain not uncommonly is poorly responsive to NSAIDs and narcotics
Neurologic	Headache (especially migraine), presyncope and/or syncope, peripheral (usually distal) sensory and/or motor neuropathies including paresthesias, tics, tremors (typically resting), chronic inflammatory demyelinating polyneuropathy, seizure disorders (can be “treatment-refractory”)
Psychiatric	Mood disturbances (eg, anger, depression), bipolar affective disorder, attention deficit-hyperactivity disorder, post-traumatic stress disorder, other anxiety and panic disorders, psychoses, memory difficulties, word-finding difficulties, other cognitive dysfunction, wide variety of sleep disruptions
Endocrinologic/ Metabolic	Abnormal electrolytes (including magnesium) and liver function tests, delayed puberty, dysmenorrhea, endometriosis, osteosclerosis and/or osteoporosis, hypothyroidism, hyperthyroidism, dyslipidemia, hyperferritinemia, selective vitamin and/or other micronutrient deficiencies, weight change, possibly diabetes mellitus
Hematologic/ Coagulopathic	Polycythemia or anemia, leukocytosis or leukopenia, chronic (usually mild) monocytosis or eosinophilia or basophilia, thrombocytosis or thrombocytopenia, arterial and/or venous thromboembolic disease, aberrant bruising and bleeding; in MCAS the marrow usually does not show increased or even flow-cytometrically aberrant MCs and marrow histology is often interpreted as normal or as unspecified myelodysplastic/myeloproliferative syndrome; standard cytogenetic studies are almost always normal or show culture failure
Immunologic	Type I, II, III, and IV hypersensitivity reactions (eg, allergy, delayed-type hypersensitivity, etc.), increased risk for malignancy, autoimmunity, impaired healing, increased susceptibility to infection, elevated or decreased levels of one or more isotypes of immunoglobulin; modest monoclonal gammopathy of undetermined significance not uncommon

\*Most symptoms and findings are chronic and low grade; some are persistent; many are either episodic or waxing/waning.

interacting extensively with its human host<sup>28</sup> and second only to the liver as the largest metabolic organ in the body, involved in 10% of circulating metabolites,<sup>29</sup> many impacting nervous and immune system function. Recent environmental factors (eg, extensive antibiotic use, increased processed-food consumption) may underlie decreases in microbiotic diversity and metabolic

capacity, in turn altering the function of MCs which, via their proximity to nervous and endocrine system elements, crucially regulate intestinal permeability, visceral sensitivity, and gastrointestinal motility.<sup>30–34</sup>

Among key end-products of microbial fermentation of complex polysaccharides in the distal gut, short-chain fatty acids (SCFAs) (eg, butyrate, propionate,



acetate) calorically nourish colonocytes and communicate, via specific cell-surface G-protein receptors, with many host cells, including MCs.<sup>35,36</sup> SCFAs inhibit histone deacetylation, modulating cell function through epigenetic changes (a crucial mechanism for the induction of colonic regulatory forkhead box P3 [FoxP3]<sup>+</sup>CD4<sup>+</sup> T cells)<sup>37–39</sup> and inhibiting MC histamine release.<sup>40</sup> Butyrate inhibits MC degranulation and tumor necrosis factor- $\alpha$  production.<sup>41</sup>

Microbial carbohydrate products (eg, S-type lectins such as galectins and I-type lectins such as Siglecs) affect MCs. The expression of Fc $\epsilon$ RI-dependent histamine and prostaglandin D<sub>2</sub> release was blocked by the binding of microbial metabolite Siglec-8 with MCs.<sup>42</sup> MCs from galectin-3-deficient mice secrete less histamine and interleukin-4 on Fc $\epsilon$ RI cross-linking.<sup>43</sup> Extracellular galectin-3 induces apoptosis in MCs, while galectin-1 and -9 reduce the ability of MCs to degranulate, possibly due to inhibition of IgE-antigen complex formation.<sup>44</sup>

The proximity of degranulated MCs to enteric glia has engendered hypotheses that stress activates the enteric nervous system, attracting and activating MCs.<sup>29,30</sup> Stressed rats develop gastrointestinal tract mucosal MC hyperplasia.<sup>45</sup> Acute stress stimulates intestinal mucus secretion by a MC-dependent mechanism.<sup>43</sup> Stress causes rat colonic epithelial barrier defects and subsequent mucosal MC activation.<sup>46</sup> Decreased barrier function may result in greater exposure to microbiota, promoting migration of MCs into intestinal tissue.<sup>16</sup> Commensal bacteria suppress in vitro degranulation of MCs.<sup>16</sup> As reviewed by Wesolowski and Paumet,<sup>47</sup> bacteria differentially regulate secretion of MC-derived mediators. *Mycoplasma pneumoniae* and *Streptococcus pneumoniae* induce MC degranulation, whereas probiotics inhibit degranulation in human and mouse MCs. Impacts of any given bacterium likely are not so 1-sided, though. In mice, *Escherichia coli* attenuates serotonin and  $\beta$ -hexosaminidase secretion but induces histamine release. Molecular mechanisms of such modulation are largely unexplored, but Wesolowski and Paumet reported that *E coli* profoundly decreases synaptosomal-associated protein 23 phosphorylation and ternary soluble N-ethyl maleimide-sensitive fusion protein attachment protein receptor complex assembly, both required for MC granule exocytosis, thus inhibiting Fc $\epsilon$ RI-dependent degranulation.<sup>46</sup> Altered motility patterns and abdominal pain in postinfectious

IBS are associated with MC secretions such as tryptase and serotonin.<sup>48</sup> Urinary N-methylhistamine, marking MC activation, is increased in patients with IBD<sup>49</sup> and in animal models.<sup>50</sup> In rats, alcohol ingestion alters the colonic mucosal epithelial barrier via ethanol oxidation into (MC-activating) acetaldehyde by enteric microflora.<sup>51</sup> Chronic alcohol consumption modifies human gut microbiota, causing endotoxemia and immune system hyperactivation, which contribute to liver disease<sup>52</sup> and are all the more interesting in view of the frequency of hepatic abnormalities in MCAS.<sup>53</sup> Alcohol has complex effects on MCs: Alcohol-related immunosuppression may be due in part to MC inhibition<sup>54</sup> and even apoptosis<sup>15</sup> by alcohol (or its metabolites), but in some circumstances alcohol and its metabolites (or preservatives such as sulfites) activate MCs,<sup>55–57</sup> which may be unsurprising given the intolerance that many patients with MCAD have for alcohol.<sup>58,59</sup>

Dietary management is important in IBS. The most successful diet (FODMAP [fermentable oligosaccharides, disaccharides, monosaccharides, and polyols]) decreases colonic gas and SCFA production.<sup>60</sup> Many studies show increased colonic mucosa MCs in diarrhea-dominant and postinfectious IBS<sup>30,32,61–64</sup> and sometimes in constipated IBS.<sup>65</sup> Several small clinical trials suggest roles for MC stabilizers in IBS.<sup>66–68</sup>

Medications, too, affect microbiota and their MC interactions. In compensated cirrhotic patients, omeprazole is associated with microbiotic shift and functional change in distal gut, engendering bacterial overgrowth.<sup>69</sup> Compared with untreated controls, mice treated with antibiotics to reduce gut microbiota and then exposed to *Aspergillus* spp developed increased MCs.<sup>70</sup> Amoxicillin-induced microbiotic changes reduce the expression of major histocompatibility complex class I and II genes in the small and large intestines, reduce adenosine monophosphate expression in the proximal intestine, and increase MC protease expression in the distal small intestine.<sup>71</sup> Mouse microbiotic alterations from broad-spectrum antibiotics or germ-free conditions cause a switch from IgA to IgE and subsequent MC activation.<sup>72</sup>

Microbiotic manipulations can reduce normal MC activation. The probiotic lysate significantly inhibits capsaicin-induced calcitonin gene-related peptide release by neurons and improves signs of inflammation.<sup>73</sup> A humanized mouse model fed high fat plus

probiotics exhibited significantly fewer intestinal MCs and multiple other antiinflammatory effects compared with identical mice not provided probiotics.<sup>74</sup> There are increasing suggestions, too, that microbiotic manipulations may be able to prevent colorectal cancer,<sup>75</sup> an effect possibly dependent on microbiotic interactions with MCs and perhaps unsurprising given not only long-recognized associations between MC activation and initiation and progression of cancer<sup>76,77</sup> but also an ability to improve outcomes of human malignancies on recognition and treatment of comorbid SM<sup>78</sup> or MCAS.<sup>79</sup>

Beyond the gut are microbiota of the skin, lungs, sinuses, and mouth. The involvement of MCs in these other networks is just beginning to be defined. Germ-free mutant animal models expressed significantly higher levels of thymic stromal lymphopoietin, a major proinflammatory cytokine (and MC mediator) released by disrupted skin, suggesting roles for microbiota in ameliorating keratinocyte stress signals.<sup>80</sup> Commensal bacterial lipoteichoic acid increases skin MC antimicrobial activity against vaccinia viruses.<sup>81</sup> Healthy lung features microbiota different from those of diseased lung.<sup>82</sup> Microbiota-induced bronchial epithelial thymic stromal lymphopoietin production, in turn, induces MC production of mediators pivotal in asthma development.<sup>68</sup> Diet-influenced shift in murine lung microbiota increases circulating SCFAs and protects against allergic pulmonary inflammation.<sup>83</sup> Bacterial virulence factors such as lipoteichoic acid, lipopolysaccharides, and peptidoglycans stimulate the secretion of IL-1 $\beta$ , tumor necrosis factor- $\alpha$ , IL-6, and IL-8 by epithelial and other gingival cells including MCs, and then further diffusion of these and other cytokines into gingival connective tissue directly or indirectly stimulates many cells including MCs.<sup>84</sup>

Little is known about how dysfunctional MCs interact with microbiota. Given that microbiotic manipulations can reduce normal MC activation, perhaps some abnormal MCs might be similarly quiesced. MC regulation is crucially dependent on a variety of tyrosine kinases, dominantly Kit but also others, including Lyn.<sup>85</sup> Thus, Lyn dysregulation might have MC-dependent consequences. Indeed, Lyn-deficient mice develop increased microbiota-dependent intestinal inflammation and susceptibility to enteric pathogens.<sup>86</sup>

## CONCLUSIONS

Conveying a new understanding that all MC disease features inappropriate MC activation, the new top-level designation MCAD encompasses various types of rare mastocytosis and likely prevalent MCAS. The apparent uniqueness in each patient with MCAD of constitutively activating mutational patterns in KIT and other MC regulatory elements likely is the principal driver of not only the specific clinical presentation, and therapeutic response profile, in each patient but also the great heterogeneity across this population. The complex systems biology of microbiota are just beginning to be elucidated, but it is clear that there are innumerable interactions with normal MCs, creating the potential for exponentially more complex interactions with the abnormal MCs of MCAD. Much more research lies ahead.

## CONFLICTS OF INTEREST

The authors have indicated that they have no conflicts of interest with regard to the content of this article.

## REFERENCES

1. Afrin LB. The presentation, diagnosis and treatment of mast cell activation syndrome. *Curr Allergy Clin Immunol*. 2014;27:146–158.
2. Afrin L. Presentation, diagnosis, and management of mast cell activation syndrome. In: Murray D, ed. *Mast Cells: Phenotypic Features, Biological Functions, and Role in Immunity*. Happaage, NY: Nova Science Publishers; 2013:155–231. [https://www.novapublishers.com/catalog/product\\_info.php?products\\_id=42603](https://www.novapublishers.com/catalog/product_info.php?products_id=42603).
3. Crivellato E, Ribatti D. The mast cell: an evolutionary perspective. *Biol Rev Camb Philos Soc*. 2010;85:347–360. [PMID: 19961471].
4. Theoharides TC, Kempuraj D, Tagen M, et al. Differential release of mast cell mediators and the pathogenesis of inflammation. *Immunol Rev*. 2007;217:65–78. [PMID: 17498052].
5. Greenberg G, Burnstock G. A novel cell-to-cell interaction between mast cells and other cell types. *Exp Cell Res*. 1983;147:1–13. [PMID: 6617756].
6. Roberts LJ, Oates JA. Biochemical diagnosis of systemic mast cell disorders. *J Invest Dermatol*. 1991;96:19S–25S. [PMID: 16799604].
7. Sonneck K, Florian S, Müllauer L, et al. Diagnostic and subdiagnostic accumulation of mast cells in the bone marrow of patients with anaphylaxis: Monoclonal mast cell activation syndrome. *Int Arch Allergy Immunol*. 2007;142:158–164. [PMID: 17057414].
8. Akin C, Scott LM, Kocabas CN, et al. Demonstration of an aberrant mast-cell population with clonal markers in a

- subset of patients with “idiopathic” anaphylaxis. *Blood*. 2007;110:2331–2333. [PMID: 17638853].
9. Molderings GJ, Kolck UW, Scheurlen C, et al. Multiple novel alterations in Kit tyrosine kinase in patients with gastrointestinally pronounced systemic mast cell activation disorder. *Scand J Gastroenterol*. 2007;42:1045–1053. [PMID: 17710669].
  10. Molderings GJ, Meis K, Kolck UW, et al. Comparative analysis of mutation of tyrosine kinase Kit in mast cells from patients with systemic mast cell activation syndrome and healthy subjects. *Immunogenetics*. 2010;62:721–727. [PMID: 20838788].
  11. Molderings GJ. The genetic basis of mast cell activation disease—looking through a glass darkly. *Crit Rev Oncol Hematol*. 2014. S1040-8428(14)00149-8 [PMID: 25305106].
  12. Haenisch B, Nöthen MM, Molderings GJ. Systemic mast cell activation disease: the role of molecular genetic alterations in pathogenesis, heritability and diagnostics. *Immunol*. 2012;137:197–205. [PMID: 22957768].
  13. Molderings GJ, Haenisch B, Bogdanow M, et al. Familial occurrence of systemic mast cell activation disease. *PLoS One*. 2013;8:e76241. [PMID: 24098785].
  14. Haenisch B, Fröhlich H, Herms S, Molderings GJ. Evidence for contribution of epigenetic mechanisms in the pathogenesis of systemic mast cell activation disease. *Immunogenetics*. 2014;66:287–297. [PMID: 24622794].
  15. Nurmi K, Methuen T, Mäki T, et al. Ethanol induces apoptosis in human mast cells. *Life Sci*. 2009;85:678–684. [PMID: 19775596].
  16. Kasakura K, Takahashi K, Itoh T, et al. Commensal bacteria directly suppress in vitro degranulation of mast cells in a MyD88-independent manner. *Biosci Biotechnol Biochem*. 2014;78:1669–1676. [PMID: 25273132].
  17. Afrin LB, Molderings GJ. A concise, practical guide to diagnostic assessment for mast cell activation disease. *World J Hematol*. 2014;3:1–17.
  18. Picard M, Giavina-Bianchi P, Mezzano V, Castells M. Expanding spectrum of mast cell activation disorders: monoclonal and idiopathic mast cell activation syndromes. *Clin Ther*. 2013;35:548–562. [PMID: 23642289].
  19. Amon U, Hartmann K, Horny H-P, Nowak A. Mastocytosis—An update. *J Dtsch Dermatol Ges*. 2010;8:695–711. [PMID: 20678151].
  20. Cohen SS, Skovbo S, Vestergaard H, et al. Epidemiology of systemic mastocytosis in Denmark. *Br J Haematol*. 2014;166:521–528. [PMID: 24761987].
  21. Lim K-H, Tefferi A, Lasho TL, et al. Systemic mastocytosis in 342 consecutive adults: survival studies and prognostic factors. *Blood*. 2009;113:5727–5736. [PMID: 19363219].
  22. 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;2:70–76. [PMID: 24565772].
  23. Hermine O, Lortholary O, Leventhal PS, et al. Case-control cohort study of patients' perceptions of disability in mastocytosis. *PLoS One*. 2008;3:e2266. [PMID: 18509466].
  24. Escribano L, Alvarez-Twose I, Sánchez-Muñoz L, et al. Prognosis in adult indolent systemic mastocytosis: a long-term study of the Spanish Network on Mastocytosis in a series of 145 patients. *J Allergy Clin Immunol*. 2009;124:514–521. [PMID: 19541349].
  25. Pardanani A, Tefferi A. Systemic mastocytosis in adults: a review on prognosis and treatment based on 342 Mayo Clinic patients and current literature. *Curr Opin Hematol*. 2010;17:125–132. [PMID: 20075725].
  26. Valent P, Horny HP, Escribano L, et al. Diagnostic criteria and classification of mastocytosis: a consensus proposal. *Leuk Res*. 2001;25:603–625. [PMID: 11377686].
  27. Brockow K. Epidemiology, prognosis, and risk factors in mastocytosis. *Immunol Allergy Clin North Am*. 2014;34:283–295. [PMID: 24745674].
  28. Bäckhed F, Ley RE, Sonnenburg JL, et al. Host-bacterial mutualism in the human intestine. *Science*. 2005;307:1915–1920. [PMID: 15790844].
  29. Wikoff WR, Anfora AT, Liu J, et al. Metabolomics analysis reveals large effects of gut microflora on mammalian blood metabolites. *Proc Natl Acad Sci U S A*. 2009;106:3698–36703. [PMID: 19234110].
  30. Konturek PC, Brzozowski T, Konturek SJ. Stress and the gut: pathophysiology, clinical consequences, diagnostic approach and treatment options. *J Physiol Pharmacol*. 2011;62:591–599. [PMID: 22314561].
  31. Park CH, Joo YE, Choi SK, et al. Activated mast cells infiltrate in close proximity to enteric nerves in diarrhea-predominant irritable bowel syndrome. *J Korean Med Sci*. 2003;18:204–210. [PMID: 12692417].
  32. Schaeffer DF, Kirsch R, Riddell RH. Mast cells and intestinal motility disorders (mastocytic enteritis/colitis). *Dig Dis Sci*. 2012;57:1118–1121. [PMID: 22466075].
  33. Lee KJ, Kim YB, Kim JH, et al. The alteration of enterochromaffin cell, mast cell, and lamina propria T lymphocyte numbers in irritable bowel syndrome and its relationship with psychological factors. *J Gastroenterol Hepatol*. 2008;23:1689–1694. [PMID: 19120860].
  34. Bischoff SC, Krämer S. Human mast cells, bacteria, and intestinal immunity. *Immunol Rev*. 2007;217:329–337. [PMID: 17498069].
  35. Maslowski KM, Vieira AT, Ng A, et al. Regulation of inflammatory responses by gut microbiota and chemoattractant receptor GPR43. *Nature*. 2009;461:1282–1286. [PMID: 19865172].
  36. Tazoe H, Otomo Y, Karaki S, et al. Expression of short-chain fatty acid receptor GPR41 in the human colon. *Biomed Res*. 2009;30:149–156. [PMID: 19574715].

37. Smith PM, Howitt MR, Panikov N, et al. The microbial metabolites, short-chain fatty acids, regulate colonic Treg cell homeostasis. *Science*. 2013;341:569–573. [PMID: 23828891].
38. Furusawa Y, Obata Y, Fukuda S, et al. Commensal microbe-derived butyrate induces the differentiation of colonic regulatory T cells. *Nature*. 2013;504:446–450. [PMID: 24226770].
39. Arpaia N, Campbell C, Fan X, et al. Metabolites produced by commensal bacteria promote peripheral regulatory T-cell generation. *Nature*. 2013;504:451–455. [PMID: 24226773].
40. Peh KH, Wan BY, Assem ES, et al. Mode of action of histone deacetylase inhibitors on mast cell histamine release and colon muscle contraction. *Inflamm Res*. 2009;58:24–25. [PMID: 19271129].
41. Diakos C, Prieschl EE, Säemann MD, et al. n-Butyrate inhibits Jun NH(2)-terminal kinase activation and cytokine transcription in mast cells. *Biochem Biophys Res Commun*. 2006;349:863–868. [PMID: 16949031].
42. Yokoi H, Choi OH, Hubbard W, et al. Inhibition of FcεRI-dependent mediator release and calcium flux from human mast cells by sialic acid-binding immunoglobulin-like lectin 8 engagement. *J Allergy Clin Immunol*. 2008;121:e1–505. e1 [PMID: 18036650].
43. Chen HY, Sharma BB, Yu L, et al. Role of galectin-3 in mast cell functions: galectin-3-deficient mast cells exhibit impaired mediator release and defective JNK expression. *J Immunol*. 2006;177:4991–4997. [PMID: 17015681].
44. Cerliani JP, Stowell SR, Mascanfroni ID, et al. Expanding the universe of cytokines and pattern recognition receptors: galectins and glycans in innate immunity. *J Clin Immunol*. 2011;31:10–21. [PMID: 21184154].
45. Söderholm JD, Yang PC, Ceponis P, et al. Chronic stress induces mast cell-dependent bacterial adherence and initiates mucosal inflammation in rat intestine. *Gastroenterology*. 2002;123:1099–1108. [PMID: 12360472].
46. Santos J, Yang PC, Söderholm JD, et al. Role of mast cells in chronic stress induced colonic epithelial barrier dysfunction in the rat. *Gut*. 2001;48:630–636. [PMID: 11302959].
47. Wesolowski J, Paumet F. *Escherichia coli* exposure inhibits exocytic SNARE-mediated membrane fusion in mast cells. *Traffic*. 2014;15:516–530. [PMID: 24494924].
48. Cenac N, Andrews CN, Holzhausen M, et al. Role of protease activity in visceral pain in irritable bowel syndrome. *J Clin Invest*. 2007;117:636–647. [PMID: 17304351].
49. Lu K, Knutson CG, Wishnok JS, et al. Serum metabolomics in a *Helicobacter hepaticus* mouse model of inflammatory bowel disease reveal important changes in the microbiome, serum peptides, and intermediary metabolism. *J Proteome Res*. 2012;11:4916–4926. [PMID: 22957933].
50. Winterkamp S, Weidenhiller M, Otte P, et al. Urinary excretion of N-methylhistamine as a marker of disease activity in inflammatory bowel disease. *Am J Gastroenterol*. 2002;97:3071–3077. [PMID: 12492192].
51. Ferrier L, Bérard F, Debrauwer L, et al. Impairment of the intestinal barrier by ethanol involves enteric microflora and mast cell activation in rodents. *Am J Pathol*. 2006;168:1148–1154. [PMID: 16565490].
52. Malaguarnera G, Giordano M, Nunnari G, et al. Gut microbiota in alcoholic liver disease: pathogenic role and therapeutic perspectives. *World J Gastroenterol*. 2014;20:16639–16648. [PMID: 25469033].
53. Alfter K, von Kügelgen I, Haenisch B, et al. New aspects of liver abnormalities as part of the systemic mast cell activation syndrome. *Liver Int*. 2009;29:181–186. [PMID: 18662284].
54. Vally H, Thompson PJ. Allergic and asthmatic reactions to alcoholic drinks. *Addict Biol*. 2003;8:3–11. [PMID: 12745410].
55. Ruiz CM, Gomes JC. Effects of ethanol, acetaldehyde, and acetic acid on histamine secretion in guinea pig lung mast cells. *Alcohol*. 2000;20:133–138. [PMID: 10719792].
56. Gui XY. Mast cells: a possible link between psychological stress, enteric infection, food allergy and gut hypersensitivity in the irritable bowel syndrome. *J Gastroenterol Hepatol*. 1998;13:980–989. [PMID: 9835312].
57. Adams KE, Rans TS. Adverse reactions to alcohol and alcoholic beverages. *Ann Allergy Asthma Immunol*. 2013;111:439–445. [PMID: 24267355].
58. Bain BJ. Systemic mastocytosis and other mast cell neoplasms. *Br J Haematol*. 1999;106:9–17. [PMID: 10444157].
59. Topar G, Staudacher C, Geisen F, et al. Urticaria pigmentosa: a clinical, hematopathologic, and serologic study of 30 adults. *Am J Clin Pathol*. 1998;109:279–285. [PMID: 9495199].
60. Halmos EP, Power VA, Shepherd SJ, et al. A diet low in FODMAPs reduces symptoms of irritable bowel syndrome. *Gastroenterology*. 2014;146:e5. [PMID: 24076059].
61. O'Sullivan M, Clayton N, Breslin NP, et al. Increased mast cells in the irritable bowel syndrome. *Neurogastroenterol Motil*. 2000;12:449–457. [PMID: 11012945].
62. Piche T, Saint-Paul MC, Dainese R, et al. Mast cells and cellularity of the colonic mucosa correlated with fatigue and depression in irritable bowel syndrome. *Gut*. 2008;57:468–473. [PMID: 18194987].
63. Walker MM, Talley NJ, Prabhakar M, et al. Duodenal mastocytosis, eosinophilia and intraepithelial lymphocytosis as possible disease markers in the irritable bowel syndrome and functional dyspepsia. *Aliment Pharmacol Ther*. 2009;29:765–773. [PMID: ].
64. Guilarte M, Santos J, de Torres I, et al. *Gut*. 2007;56:203–209. [PMID: 17005763].
65. Bassotti G, Villanacci V, Nascimbeni R, et al. Increase of colonic mast cells in



- obstructed defecation and their relationship with enteric glia. *Dig Dis Sci*. 2012;57:65–71. [PMID: 21814802].
66. Stefanini GF, Saggioro A, Alvisi V, et al. Oral cromolyn sodium in comparison with elimination diet in the irritable bowel syndrome, diarrheic type. Multicenter study of 428 patients. *Scand J Gastroenterol*. 1995;30:535–541. [PMID: 7569760].
  67. Corinaldesi R, Stanghellini V, Cremon C, et al. Effect of mesalazine on mucosal immune biomarkers in irritable bowel syndrome: a randomized controlled proof-of-concept study. *Aliment Pharmacol Ther*. 2009;30:245–252. [PMID: 19438846].
  68. Klooker TK, Braak B, Koopman KE, et al. The mast cell stabiliser ketotifen decreases visceral hypersensitivity and improves intestinal symptoms in patients with irritable bowel syndrome. *Gut*. 2010;59:1213–1221. [PMID: 20650926].
  69. Bajaj JS, Cox LJ, Betrapally NS, et al. Systems biology analysis of omeprazole therapy in cirrhosis demonstrates significant shifts in gut microbiota composition and function. *Am J Physiol Gastrointest Liver Physiol*. 2014;307:G951–G957. [PMID: 25258407].
  70. Noverr MC, Noggle RM, Toews GB, Huffnagle GB. Role of antibiotics and fungal microbiota in driving pulmonary allergic responses. *Infect Immun*. 2004;72:4996–5003. [PMID: 15321991].
  71. Ubeda C, Pamer EG. Antibiotics, microbiota, and immune defense. *Trends Immunol*. 2012;33:459–466. [PMID: 22677185].
  72. Cahenzli J, Köller Y, Wyss M, et al. Intestinal microbial diversity during early-life colonization shapes long-term IgE levels. *Cell Host Microbe*. 2013;14:559–570. [PMID: 24237701].
  73. Guéniche A, Bastien P, Ovigne JM, et al. *Bifidobacterium longum* lysate, a new ingredient for reactive skin. *Exp Dermatol*. 2010;19:e1–e8. [PMID: 19624730].
  74. Oksaharju A, Kooistra T, Kleemann R, et al. Effects of probiotic *Lactobacillus rhamnosus* GG and *Propionibacterium freudenreichii* ssp. *shermanii* JS supplementation on intestinal and systemic markers of inflammation in ApoE\*3Leiden mice consuming a high-fat diet. *Br J Nutr*. 2013;110:77–85. [PMID: 23211714].
  75. Uccello M, Malaguarnera G, Basile F, et al. Potential role of probiotics on colorectal cancer prevention. *BMC Surg*. 2012;12:S35. [PMID: 23173670].
  76. Galinsky DS, Nechushtan H. Mast cells and cancer – no longer just basic science. *Crit Rev Oncol Hematol*. 2008;68:115–130. [PMID: 18632284].
  77. Ryan JJ, Fernando JF. Mast cell modulation of the immune response. *Curr Allergy Asthma Rep*. 2009;9:353–359. [PMID: 19671378].
  78. Valent P, Sperr WR, Akin C. How I treat patients with advanced systemic mastocytosis. *Blood*. 2010;116:5812–5817. [PMID: 20855864].
  79. Afrin LB, Spruill LS, Schabel SI, Young-Pierce JL. Improved metastatic uterine papillary serous cancer outcome with treatment of mast cell activation syndrome. *Oncology (Williston Park)*. 2014;28:134. [PMID: 24701700].
  80. Yockey LJ, Demehri S, Turkoz M, et al. The absence of a microbiota enhances TSLP expression in mice with defective skin barrier but does not affect the severity of their allergic inflammation. *J Invest Dermatol*. 2013;133:2714–2721. [PMID: 23698100].
  81. Wang Z, MacLeod DT, Di Nardo A. Commensal bacteria lipoteichoic acid increases skin mast cell antimicrobial activity against vaccinia viruses. *J Immunol*. 2012;189:1551–1558. [PMID: 22772452].
  82. Edwards MR, Bartlett NW, Hussell T, et al. The microbiology of asthma. *Nat Rev Microbiol*. 2012;10:459–471. [PMID: 22669219].
  83. Trompette A, Gollwitzer ES, Yadava K, et al. Gut microbiota metabolism of dietary fiber influences allergic airway disease and hematopoiesis. *Nat Med*. 2014;20:159–166. [PMID: 24390308].
  84. Araujo M. Chronic kidney disease as a modifier of the periodontitis-associated microbiome and the response to periodontal therapy. *Master's Theses, University of Connecticut*. 2013. Paper 452. [http://digitalcommons.uconn.edu/gs\\_theses/452](http://digitalcommons.uconn.edu/gs_theses/452).
  85. Gleixner KV, Mayerhofer M, Cerny-Reiterer S, et al. KIT-D816V-independent oncogenic signaling in neoplastic cells in systemic mastocytosis: role of Lyn and Btk activation and disruption by dasatinib and bosutinib. *Blood*. 2011;118:1885–1898. [PMID: 21680801].
  86. Roberts ME, Bishop JL, Fan X, et al. Lyn deficiency leads to increased microbiota-dependent intestinal inflammation and susceptibility to enteric pathogens. *J Immunol*. 2014;193:5249–5263. [PMID: 25339668].

---

**Address for correspondence:** Lawrence B. Afrin, MD, Division of Hematology, Oncology, and Transplantation, University of Minnesota, 420 Delaware Street SE, MMC 480, Minneapolis, MN 55455. E-mail: afrinl@umn.edu