Special Article

Mast Cell Diseases in Practice and Research: Issues and Perspectives Raised by Patients and Their Recommendations to the Scientific Community and Beyond

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BACKGROUND: Since 2010, patients and physicians have collaborated to understand unmet needs of patients with mast cell diseases, incorporating mastocytosis and mast cell activation disorders, which include mast cell activation syndromes.
OBJECTIVE: This Open Innovation in Science project aims to expand understanding of the needs of patients affected by mast cell diseases, and encourage global communication among patient advocacy groups, physicians, researchers, industry, and government. A major aim is to support the scientific community's efforts to improve diagnosis, management, therapy, and patients' quality of life by addressing unmet needs.
METHODS: In collaboration with mast cell disease specialists, 13 patient advocacy groups from 12 countries and regions developed lists of top patient needs. A core team of leaders from patient advocacy groups collected and analyzed the data and proposed possible actions to address patient needs.
RESULTS: Findings identified similarities and differences among participating countries in unmet needs between patients

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Abbreviations used

AIM- American Initiative in Mast Cell Diseases
CoE/RC- Centers of excellence/reference centers
ECNM- European Competence Network on Mastocytosis
HαT- Hereditary α-tryptasemia
HCP- Health care professional
ICD-10-CM- International Classification of Diseases, 10th Revision, Clinical Modification
ICD-11- International Classification of Diseases, 11th Revision
MC- Mast cell
MCAD- Mast cell activation disorders
MCAS- Mast cell activation syndromes
MCD- Mast cell disease
OIS- Open Innovation in Science
PAG- Patient advocacy group
QoL- Quality of life
SoC- Standards of care
WHO- World Health Organization

with mastocytosis and those with mast cell activation syndromes. Issues emphasized struggles relating to the nature and rarity of mast cell diseases, their impact on quality of life, the diagnostic process, access to appropriate care, more effective treatment, and the need for research.

CONCLUSIONS: Solutions vary across countries because situations differ, in particular regarding the existence of and access to centers of excellence and reference centers. Multifaceted mast cell activation syndrome barriers necessitate innovative approaches to improve access to appropriate care. The outcomes of this project should greatly support scientists and clinicians in their efforts to improve diagnosis, management, and treatment of patients with mastocytosis and mast cell activation disorders. **(J Allergy Clin Immunol Pract 2022;10:2039-51)**

Key words: Mastocytosis; Mast cell activation syndromes; Mast cell disorder/disease; Unmet needs; Patient perceptions and experiences; Triggers and symptoms; Anaphylaxis; Quality of life; Advocacy; Rare disease

INTRODUCTION

Mast cell diseases (MCDs) incorporate mastocytosis and mast cell activation disorders (MCAD), including mast cell activation syndromes (MCAS) (see Figure E1 in this article's Online Repository at www.jaci-inpractice.org).[1,2] Mastocytosis is a rare disease defined by abnormal mast cell (MC) accumulation only in skin (cutaneous mastocytosis) or in multiple organs (systemic mastocytosis).[1,3] These mastocytosis variants range from nonaggressive to progressive/aggressive, with differing outcome potentials.[1,4-6] Inappropriate MC activation characterizes MCAD. When symptoms are severe and recurrent, and MCAS criteria are fulfilled, MCAS is diagnosed.[1,7,8] Mast cell diseases affect all ages. They may be influenced by disease-modifying genetic traits, including hereditary α-tryptasemia (HαT),[9] and by comorbidities (eg, IgE-dependent allergies, hypersensitivity disorders, certain inflammatory diseases or immune and hematologic disorders).[1,10-12] A potential relationship of MCAS and HαT to other conditions, such as dysautonomia, connective tissue diseases, or immunodeficiency, is under investigation.[11-15] These conditions should be considered in the differential diagnosis. Mast cell diseases can have unpredictable, disabling, episodic, or chronic symptoms, including anaphylaxis, resulting from trigger exposure and MC mediator release.[3,5,16,17] Because of the range of symptom severity in MCAD, therapies should be targeted accordingly.[18] Triggers (eg, food, drugs, venoms, inhalant, physical stimuli, exercise, stress, infections, inflammatory or neoplastic diseases) may be both IgE- and non-IgE–mediated, are patient-specific, and should be

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evaluated by an allergist/immunologist.[2,19,20] Patients with more than one MCD may have increased risk for life-threatening anaphylaxis.[1,8,21] Average reported times from symptom onset to diagnosis vary substantially (4-12 years) owing to heterogeneous symptoms, lack of awareness by physicians, and lack of objective diagnostic markers.[17,22] Mast cell diseases can be psychosocially isolating and significantly reduce quality of life (QoL).[17,23-26]

Collaborative partnerships among physicians, patients, and other stakeholders (patient advocacy groups [PAGs], schools, etc) are crucial for improving QoL. Physicians' ability to address patients' medical and psychosocial needs accurately can be enhanced by understanding patient experiences and perspectives. This awareness can positively influence physician/scientist networks that develop standards of care (SoC), scientific and industry/pharmaceutical partners advancing novel therapies, and government entities establishing and revising health policy.

In 2010, MCD specialists from the European Competence Network on Mastocytosis (ECNM)[27,28] and United States, and one European Union and one US PAG, collaborated to share experiences and perspectives and to identify unmet needs of patients with mastocytosis and MCAS.[8,29,30] Each PAG combined needs for patients with mastocytosis/MCAS into top 10 lists.[8] Tremendous research and clinical advancements focused on MC activation and MCAS occurred between 2010 and 2020. Therefore, this 2010 Open Innovation in Science (OIS)[31] collaboration has been expanded to include separate lists for mastocytosis and MCAS.

Patient advocacy group representatives from Germany, Italy, Spain, the United Kingdom, the United States, and Australasia, working with physician advisors, presented top 10 lists of unmet needs for patients with mastocytosis and MCAS or participated in the 2020 ECNM annual meeting. This enhanced communication between patients and ECNM/American Initiative in Mast Cell Diseases (AIM)[32] physicians preceded the 2020 MCD Working Conference, incorporating patient perspectives into consensus criteria and classifications.[1] Additional PAG members of the International Mastocytosis and MCD Awareness Day Committee (Awareness Day Committee[33])[34] were subsequently invited to present a more global perspective.

The OIS physician perspective summary was published with the recent MCD consensus proposal.[1] Here, the individual PAG lists of patient-identified needs were analyzed, major national and international needs were categorized into topic areas, and potential actions and solutions were suggested by PAG leading authors with 93 collective years of MCD advocacy, to provide the patient perspective (see the Introduction section of the Appendix, in this article's Online Repository at www.jaci-inpractice.org for additional background). The data included are needed to align patient needs with physician goals to develop patient-reported outcomes measures and an MCD research strategy to improve SoC and quality of delivered care. Some medical systems are increasingly driven by payors and accreditation agencies, whose value-based metrics consider the patient voice to be important. By identifying patient needs, PAGs and physicians can ensure patient and clinician goals are aligned to develop meaningful endpoints advancing clinical care and critical research.

METHODS

We identified PAGs through prior engagement with ECNM/AIM, the Awareness Day Committee, or MCD physicians. Project participation required being an official MCD PAG within their country with an MCD expert physician advisor.

The project included a stepwise approach consisting of (1) invitations to PAGs to submit lists of patient-identified issues, needs, questions, concerns, wishes, visions, suggestions, and recommendations, with separate lists for mastocytosis and MCAS (one for each disease, per country), and flexibility regarding list creation methodologies; (2) presentation during the 2020 ECNM annual meeting; and (3) list submission by additional participating countries and regions, with all lists collected by the coordinating core group of PAG leaders and physician advisors.[1] The core group included leaders from four PAGs: the United States (C.C.F., S.V.J., and V.M.S.), the United Kingdom (J.S.H.), Spain (M.M.M.), and Australasia (K.A.S.).

Thirteen PAGs, representing 12 countries and regions, participated and provided lists (see Tables E1 and E2, in this article's Online Repository at www.jaci-inpractice.org). List generation methodologies varied, but all involved patients or patient representatives familiar with requested information. Some PAGs employed patient and caregiver surveys (Italy, Mexico, Netherlands, Spain, the United Kingdom, and the United States), whereas others incorporated patient requests and responses (Australasia, Austria, France, Germany (two PAGs), Poland, and Romania). Patient advocacy groups then created lists based on this patient-provided information. Some but not all PAGs ranked their points. The core group analyzed the PAG-generated lists, identified common and country-specific themes, which are the topics used in Figure 1, and explored possible solutions (additional details are provided in the Methods section of the Appendix). Although we use the term "PAGs," ultimately, these are patient-expressed needs. Discussion of diagnoses, symptoms, and triggers include those that are both patient-reported and physician-confirmed.

RESULTS

Figure 1 presents unmet need topics and commonalities/differences by country and/or region. Individual country and/or region lists are presented in Tables E1 and E2).

Shortage of MCD-proficient health care professionals

A primary need noted by most PAGs was to increase the numbers of MCD-proficient health care professionals (HCPs) to decrease referral time or time to diagnosis and improve disease management. Critical MCD educational areas identified include symptom recognition, inclusion in differential diagnosis, diagnostic criteria, trigger identification, and the use of effective treatments. Several groups requested improved communication between local and specialty physicians and between physician and patient, noting that patients sometimes felt physicians disregarded their concerns.

Centers of excellence/reference centers, multispecialty networks, patient registries, and related topics

Most PAGs suggested adding centers of excellence/reference centers (CoE/RCs), involving all related specialties to provide well-coordinated, multidisciplinary care, and developing national CoE/RC certification programs. The creation or expansion of national and international multispecialty networks, and enhanced international communication and collaboration among physician networks and PAGs regarding research, support, and advocacy were encouraged. Development of MCD patient registries, incorporating QoL data, and the use of electronic health applications to improve diagnosis and care and share research data were identified as additional important actions.

PATIENT REPORTED ISSUES/NEEDS BY TOPICS	AU	AT	FR	DE *	IT	MX	NL	PL	RO	ES	UK	US
Shortage of MCD-proficient health care professionals	● ○	●	● ○	● ○	● ○	●	●	● ○	●	● ○	● ○	● ○
Shortage of CoE/RC; Establish multidisciplinary teams to coordinate patient care	●	● ○		● ○	●	●				● ○	● ○	● ○
Expand national/international multi-specialty networks, research, support, advocacy collaboration, and further develop e-health applications				● ○						● ○		● ○
National patient registries					●							● ○
Access to appropriate care (generally)		● ○	● ○	● ○		●		● ○	●		● ○	○
- Medications	● ○	● ○	● ○			●	●	● ○	●	● ○	● ○	● ○
- Mental health care	● ○	● ○	● ○			●		● ○	●		● ○	● ○
- Skilled emergency care	●	● ○	● ○	●	●	●		●	●	● ○	● ○	● ○
Established, universally recognized MCAS diagnostic criteria	○	○	○	○	○					○	○	○
Improved diagnostic process and prognosis	● ○	● ○	○	● ○	○	●		○		● ○	● ○	○
National and international MCD standards of care		● ○	● ○	●	○		●	● ○		○	● ○	● ○
More effective treatments	● ○	● ○	● ○	● ○	● ○	●	●	● ○	●	● ○	● ○	● ○
Recognition of trigger diversity					● ○			●			● ○	● ○
Acknowledge symptom heterogeneity			●	○	○		●	○		● ○		○
Develop care plans for children		●					●	●				●
Provide comprehensive information for patients/families	● ○		● ○	● ○	● ○	●	●	●			● ○	
Promote expansion and impact of patient support/advocacy groups		● ○						●	●			
Educate society about MCDs	○			●			●	●	●			● ○
Advancement of research	● ○	● ○	● ○	● ○	● ○		●	● ○	●	● ○	● ○	● ○

● mastocytosis
○ mast cell activation syndromes (MCAS)
* Represented by two patient advocacy groups (PAGs), one for mastocytosis and one for MCAS

AU, Australasia; AT, Austria; FR, France; DE, Germany; IT, Italy; MX, Mexico; NL, Netherlands (the); PL, Poland; RO, Romania; ES, Spain; UK, United Kingdom; US, United States of America; MCAS, mast cell activation syndromes; MCD, mast cell disease; CoE/RC, Centers of Excellence/Reference Centers; E, electronic; PAG, patient advocacy groups.

Topics are presented without hierarchy. PAGs from MX, NL and RO did not submit lists for MCAS. *See text in Results section for further description of topics.*

If a PAG did not identify an issue as a top critical need, the relevant field is left blank. Please note that an empty field does not mean that the country/region is not concerned about the given issue, but rather due to the process of data collection, it may not have been identified as a top concern.

FIGURE 1. Unmet need topics commonly reported for mastocytosis and mast cell activation syndromes within lists submitted by patient advocacy groups participating in the Open Innovation in Science Mast Cell Disease project.

Enhance access to appropriate care

Affordable and accessible care were prioritized, including country-specific health and insurance system coverage of diagnostic and routine testing and treatment, and financial assistance. When care is centralized to one city in a large country, travel costs may hinder access. Patients reported difficulties identifying experienced physicians to manage and treat MCDs. They requested extended consultations to give comprehensive histories, personalized treatment plans, and registered dietician/nutritionist referrals. Many PAGs identified a need for psychological management and therapy owing to significant disease challenges and the impact on QoL, including trauma from actual or potential trigger exposure. Germany requested access to inpatient MCAS diagnosis and treatment.

Patients requested improved global access to clinical trials; a reliable supply of affordable, essential MCD medications (eg, epinephrine, ketotifen, cromolyn sodium [sodium cromoglycate], histamine receptor 2-antihistamines), including novel, targeted therapies; alternative treatments; and drugs for compassionate use. Medication withdrawals from the market were also identified as problematic; replacement options are needed. Assurance of regular access to specific medication brands and formulations was requested to prevent possible reactions.

Access to emergency care from HCPs trained to recognize and treat MCD emergencies, the implementation of national emergency department protocols and guidelines, and recognition of less frequently seen presentations of anaphylaxis were requested. A patient-accessible phone number for critical medical support during MCD emergencies and a European Union—recognized patient identification card were suggested potential measures.

Consensus criteria for diagnosing MCAS

The need for established, universally recognized and applied diagnostic criteria and algorithms for MCAS was conveyed. Patients requested that MCAS criteria be accepted by national and global health authorities (ie, the World Health Organization [WHO]), allowing for MCAS-specific SoC development, and the incorporation of US MCAS International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) codes[1] into the WHO International Classification of Diseases, 11th Revision (ICD-11) system.

Diagnostic process and prognosis

One critical goal is hastening accurate diagnosis. Patients requested better access to testing, more precise sensitive diagnostic tests, and improved prognostication. The development of novel, validated markers and tests for MC mediator release was highlighted. Requests for a holistic MCAS diagnostic approach included a thorough review of patients' signs, symptoms, and medical history through dynamic physician and patient communication.

National and international SoC for MCDs

Multiple groups highlighted the need to create and implement widely accepted, comprehensive, national, and international SoCs, incorporating QoL considerations into diagnostic approaches, management, and therapeutic algorithms. Specifically, anesthesia management, emergency care, routine vaccinations, and the COVID-19 impact were noted. Requests included improved communication regarding medical care pathways (France), guidelines for the use of MCAS anti-mediator therapy (Italy), and rehabilitation center guidelines (Germany).

Develop more effective treatments

Increased global, collaborative, funded research (see Box E1, research requested, in this article's Online Repository at www.jaci-inpractice.org) to find effective treatments to control symptoms, and curative and palliative interventions, are pressing needs. The development of targeted and/or curative therapies that include molecular or gene-based and personalized medicine approaches was highlighted (Box E1, specific signs/symptoms needing improved therapies). Challenges included the identification and management of myriad required medications and their potential side effects. Patients from Australasia, Poland, the United States, and the United Kingdom highlighted the need for further research into the impact of comorbidities (eg, how medication sensitivity or intolerance may complicate treatment).

Recognize trigger diversity

Increased public recognition and understanding of the variety of physical, environmental, and emotional patient-reported and/or physician-confirmed triggers leading to IgE- and non-IgE—mediated reactions is critical. Environmental trigger documentation, with clarification regarding vaccination and anesthesia as potential triggers, was requested. Patients reported medication ingredients as triggers. Advocacy for policies to ensure trigger-reduced environments and safer medical settings was emphasized to minimize exposures to triggers, such as cleaners, hand sanitizers, adhesives, medications, foods, and scents.

Acknowledge symptom heterogeneity

Patients reported the need for better HCP and patient awareness and improved recognition and understanding of MCD symptom heterogeneity and the impact on daily life. Misinterpretation of presenting symptoms by physicians, uncertainty regarding mastocytosis causing a given symptom, and the lack of comprehension regarding QoL reduction from debilitating fatigue (The Netherlands) were concerns.

Develop better care plans for children

Patients from four countries noted pediatric issues: QoL; access to safe, appropriate education and care (all settings and ages); support for normal physical, emotional, and psychosocial development; and staff education about epinephrine administration.

Provide comprehensive information for patients and families and promote the expansion and impact of patient support and advocacy groups

The level of understanding of MCDs can affect care and disease management. Patients requested improved, multilingual information about a variety of topics (see Box E2 in this article's Online Repository at www.jaci-inpractice.org). Collaboration among PAGs, allowing the exchange of information, mutual support, and advocacy, was prioritized, alongside the coordination of activities and improved networking to amplify the impact.

Educate society about MCDs

Societal education about MCDs to increase awareness, provide support and inclusion, prevent bullying, and advocate for trigger-reduced environments was requested. The lack of understanding about MCDs among friends, family, and colleagues was a concern.

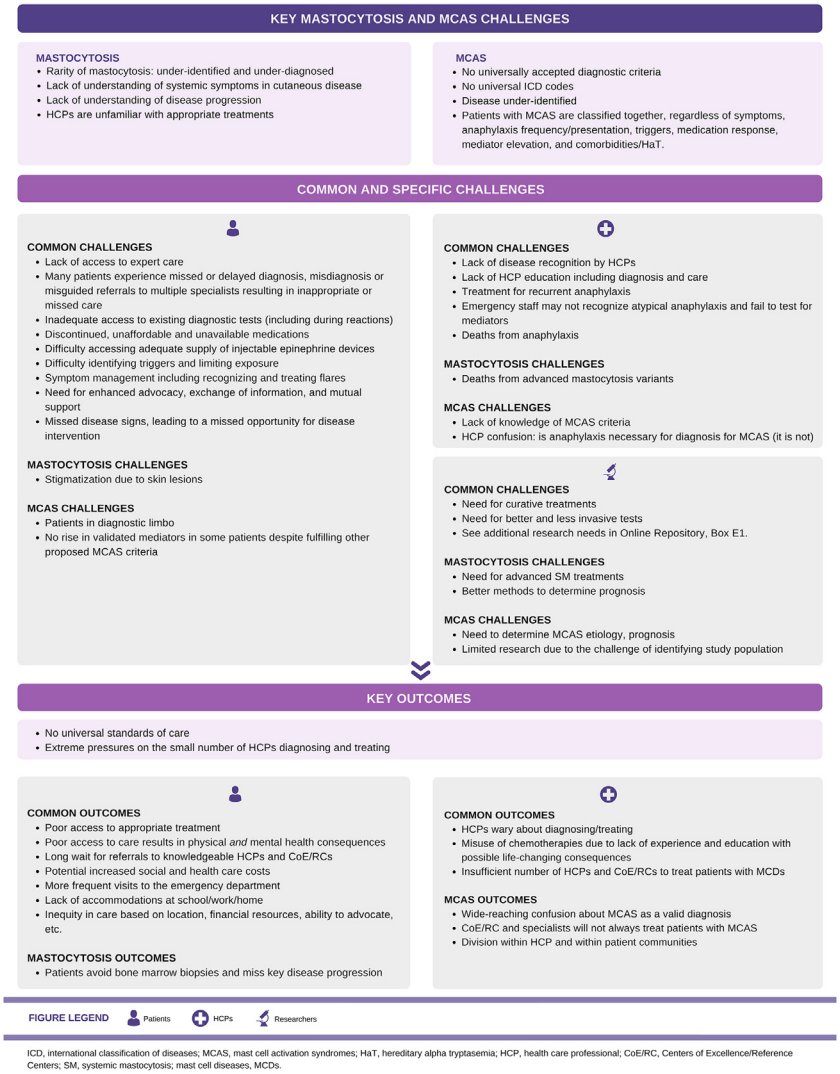


FIGURE 2. Key mastocytosis and mast cell activation syndromes (MCAS) challenges and resulting outcomes.

Research

Most lists included research needs (Box E1).

Other recommendations and concerns

See the Results section of the Appendix for additional country-specific concerns.

DISCUSSION

Despite differences between mastocytosis and MCAS, and varying levels of access to MCD care in different countries, many needs and concerns prioritized were remarkably similar and resembled those previously identified.[8,17,34] List variation may be attributed to the methods used, access to care and medication (eg, lack of CoE/RC in Australasia and Mexico), societal or HCP disease awareness, the stage of PAG development, and so on. Some lists focused on access to care, and others on research needs and improved therapies. Issues emphasized struggles related to the nature and rarity of MCDs, and the impact on QoL. Patient advocacy group–reported patient needs have been reviewed by their leading MCD specialist advisors and are not necessarily verified or shared by all of the medical community. Evidence-based assessments by physicians, using a variety of tools developed for mastocytosis or other diseases, have also identified concerns that are important to consider.[24,35,36] Figure 2 presents key MCD challenges and resulting outcomes. Additional MCD patient-reported outcomes measures are needed (see the Discussion section of the Appendix).

The OIS project aimed first to identify patient needs as a step toward seeking solutions, which may depend on the availability or specifics of existing care as well as the state of the science and funding, and may vary geographically. A comparative overview of the health care delivery systems for participating countries may be found in Figure E2 (in this article's Online Repository at www.jaci-inpractice.org). Whereas some features of the health care systems influence outcomes for rare disease patients, individual physicians can and have had an outsized and positive role in improving patient care and QoL.

Meeting patient-reported needs will require time, collaboration and a stepwise approach, such as establishing the molecular basis of MCDs before developing targeted therapies. Especially

for MCAS, multidimensional challenges require novel approaches to facilitate access to appropriate care. Broad-ranging research is needed (Box E1 and Figure 2).

Project strengths included the large number of participating countries and regions, advised by local MCD specialists, developing independent lists, and collaborative analysis by core authors. Weaknesses include variations in the phrasing of submitted points (strengths and weaknesses), nonstandardized list development methods, the nonparticipation of some invited countries, the lack of PAGs in many countries, developing country underrepresentation, and an inability to verify participating patient diagnoses. Finally, the COVID-19 pandemic affected OIS project participation, because work was initiated during the pandemic's first year.

Diagnosis and health care: issues

Many patients experience missed or delayed diagnosis, misdiagnosis, or misguided referrals to multiple specialists, or lack a prognosis[22,37-39] owing to a paucity of knowledgeable HCPs using scientifically validated diagnostic criteria,[1,17,29,30] unavailable essential diagnostic tests (eg, *KIT* D816V mutation in bone marrow or other body tissues or serum, serum tryptase, urinary mediators), and more advanced diagnostic or prognostic tests (eg, *KIT* D816V variant allele frequency[40]).[34] Some physicians believe that mastocytosis and MCAS are so rare that they are excluded from the differential diagnosis.

The ideal next step after diagnosis is to obtain MCD specialist care at CoE/RC,[39,41,42] which is currently unavailable in many locations globally. Expert care may be centralized (eg, Mexico); travel, cost, and appointment availability may be barriers to care. Some HCPs fail to grasp the complexity of mastocytosis, MCAS, HαT, and comorbidities, and may provide inappropriate management. Two-thirds of participating countries and regions noted that mental health concerns are often insufficiently addressed, as is the case globally for many diseases.[43] Mast cell mediator release can be associated with anxiety and depression, compounding some patients' ability to cope with challenging disease manifestations.[3,26]

Nearly all countries and regions highlighted emergency care as a concern (Figure 1), which varies greatly within a country. Patient-reported symptoms of mast cell activation (Figure 3) and anaphylaxis[46-50] are frequently unrecognized. Delayed or inappropriate emergency care can result in life-threatening reactions. Patients believe that they must be educators and advocates, although they fear incapability during emergencies and reactions. Expert patients are not always well-received; indeed, patients should not need to be experts, but accessing MCD specialists during a crisis is difficult. Potential triggers in medical settings present additional safety challenges.

Diagnosis and health care: possible solutions

A key solution is for MCD physician experts to establish global SoC for mastocytosis and MCAS, incorporating the impact of comorbidities and HαT.[18,51] The WHO needs to establish diagnostic criteria for MCAS. Broad, intensive education efforts by MCD experts, professional societies, and PAGs, channeled through medical school curricula and continuing medical education, are necessary to improve the diagnosis and care of MCDs. Online educational forums (eg, Project Extension for Community Healthcare Outcomes)[52] offer HCP educational opportunities.

Important educational concepts beyond those presented in the Results include prognostication for mastocytosis[53] and any information available about the potential course of MCAS, the disease impact on QoL,[17] and the complicating interplay of mastocytosis, MCAS, comorbidities, and HαT.[18,51,54] Strategies for trigger avoidance should be incorporated into treatment plans, including for chronic or episodic triggers not often observed by physicians.[29] Some accommodations may have country-specific limitations. Dissemination of research on the impacts of vaccination and anesthesia as potential triggers may be helpful.[55] Knowledgeable HCPs can mentor local physicians; both can support patients (Box E2).[34]

Formal emergency department protocols can educate staff and paramedics regarding the presentation and treatment of MC activation reactions and anaphylaxis, and speed the administration of rescue therapies. Personalized, physician-signed emergency action plans are essential. Anaphylaxis guidelines must include the recognition of less frequently seen presentations.[46,48-50] Official country-based or global identification and information cards could make travel safer.

Patient care plans should include a brief mental health assessment. A referral can be made in collaboration with the patient for support and treatment when appropriate. Ideally, ECNM, AIM, and other physician networks will invite mental health professionals into their networks and facilitate care in CoE/RC. The ECNM and AIM provide a platform for physician—researcher interaction and MCD-focused conferences. Spain requested the inclusion of additional specialties into MCD networks. At least one CoE/RC per country that is well-connected to other physicians nationally or internationally is desirable. Health care professional familiarity with all rare diseases is not realistic. A possible solution may be the creation of centralized, multidisciplinary teams to evaluate MCDs and other rare diseases and make appropriate referrals.

Access to medicines: issues

Patient advocacy groups work hard ensuring medication access, yet medication accessibility remains a concern for nearly all countries and regions. Hindrances vary across countries. Common themes include limited options and the availability of or continued access to medications, costs, no research supporting off-label use, insufficient physician education regarding appropriate medications, access to medicines and formulations compounded to avoid patients' identified allergens and triggers, and medications withdrawn from the market or formulary (noted by Australasia and France, eg, cromolyn sodium inhaler, zafirlukast). Without curative medications, access to lifesaving, symptom-reducing medications is essential.[18,51,56,57]

Cost may be a barrier to obtaining key medications. In countries where health systems centralize medication purchasing, health technology assessment—like procurement processes may block or delay access to new and expensive medications (eg, tyrosine kinase inhibitors[58,59]) (see the Discussion section of the Appendix). High prices and shortages limit access to many medications (eg, cromolyn sodium, as noted by Mexico, Poland, and Romania; as well as ketotifen and epinephrine autoinjectors, globally).

Many effective treatments for MCDs are used off-label.[56,60-63] Clinical trial data could expand cost coverage and justify formulary inclusion. For example, cromolyn sodium[56,60] has been

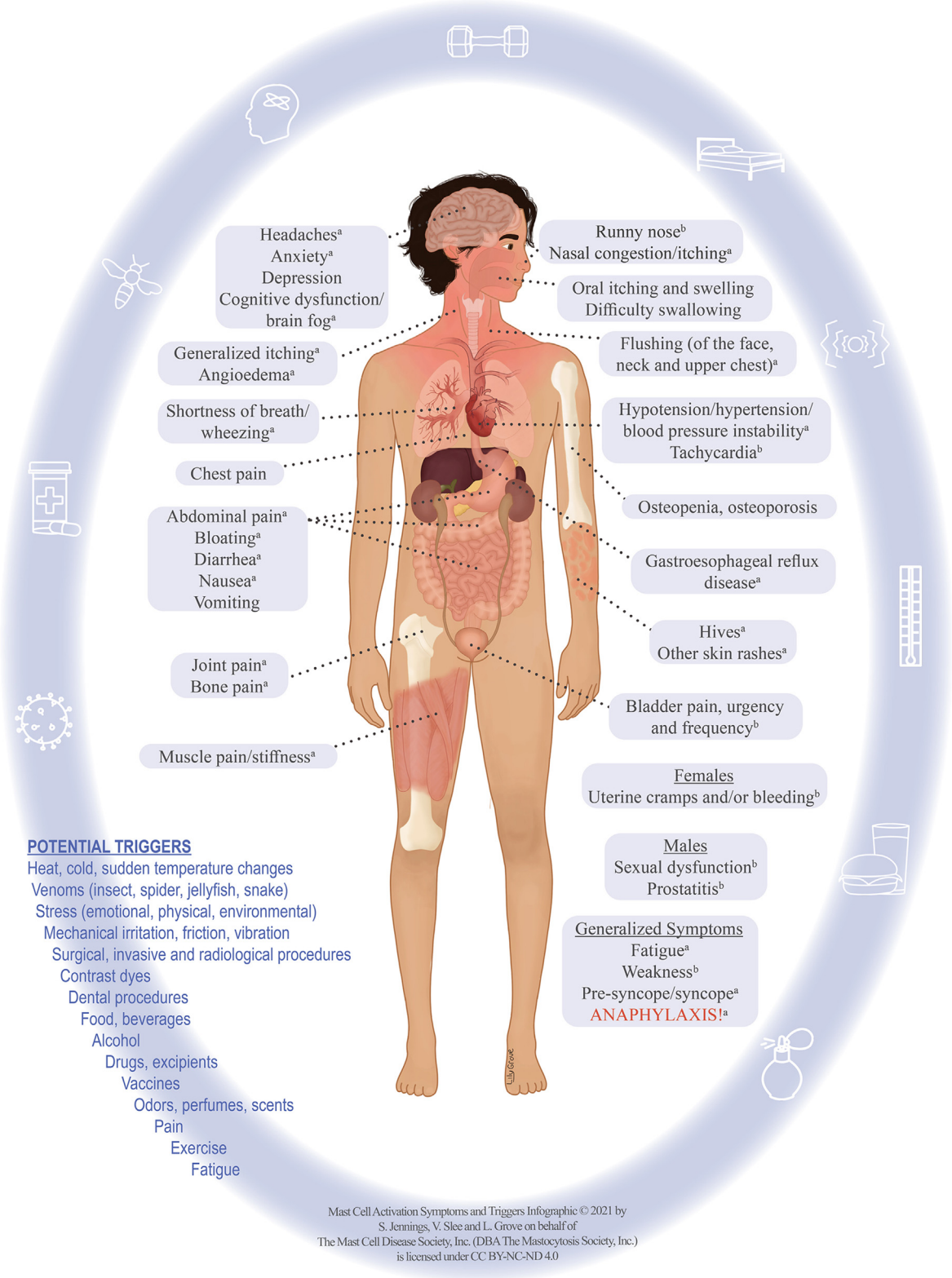
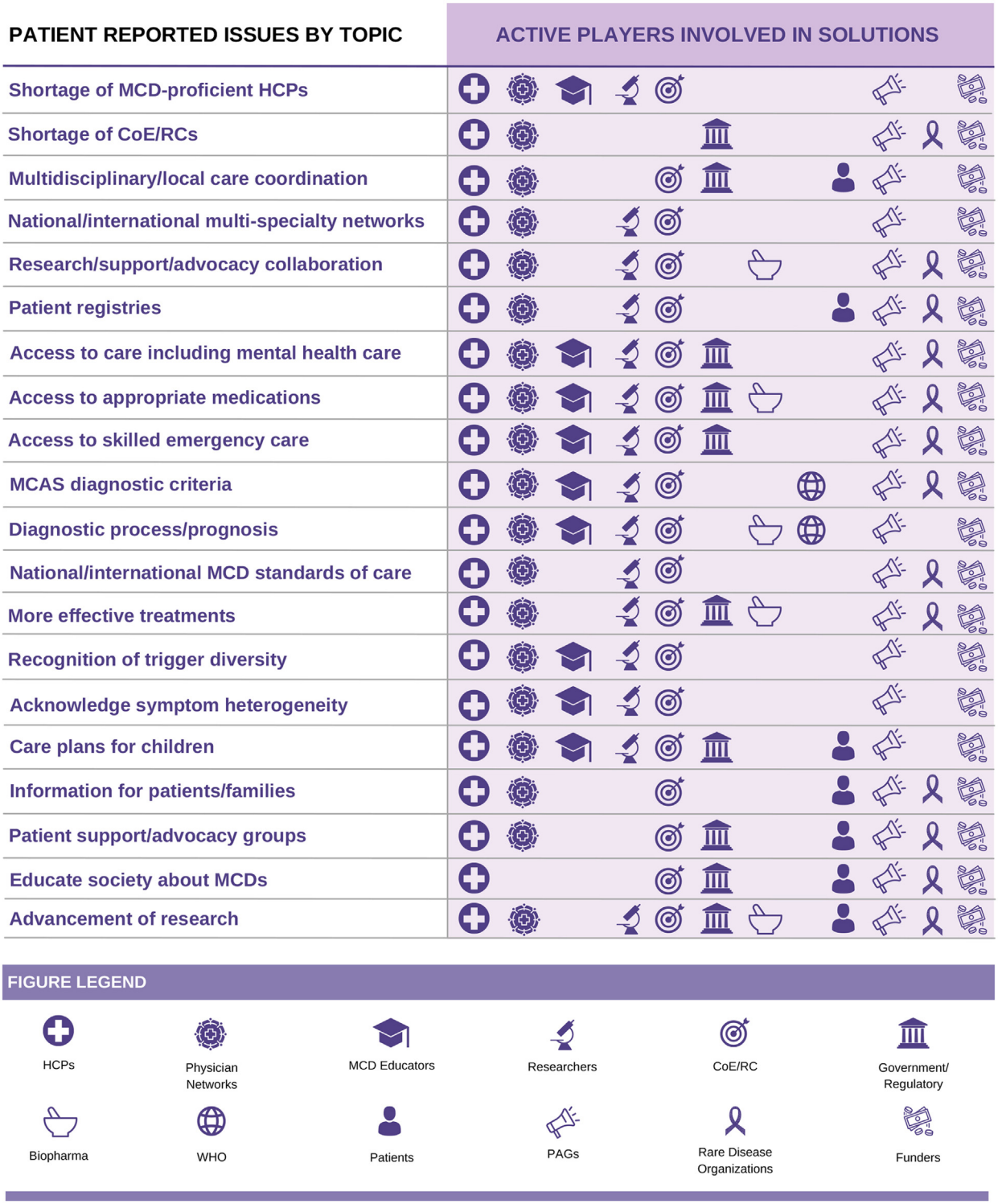


FIGURE 3. Patient-reported symptoms and triggers of mast cell activation.[16,18,44,45] Triggers/symptoms vary among individuals. [a]Symptoms reported as moderately or severely affecting greater than 45% of The Mast Cell Disease Society, Inc; DBA The Mastocytosis Society, Inc (TMS) mast cell activation syndromes (MCAS) survey respondents.[44] [b]Symptoms not included in TMS MCAS survey. Mast Cell Activation Symptoms and Triggers Infographic © 2021 printed with permission from The Mast Cell Disease Society, Inc (DBA The Mastocytosis Society, Inc).



MCD, mast cell disease; HCP, health care professional; CoE/RC, Centers of Excellence/Reference Centers; MCAS, mast cell activation syndromes; SoC, standards of care; WHO, World Health Organization; PAGs, patient advocacy groups.

FIGURE 4. Active players with a role in solutions to address unmet needs and issues of concern to patients with mast cell diseases.

approved in some countries for mastocytosis and in others for food allergy. Clinical trials are needed to support approval for MCAS. In some countries, certain antihistamines or cromolyn sodium must be imported or compounded, or are simply unavailable (see the Discussion section of the Appendix for more information and examples).

Access to medicines: possible solutions

Establishing SoC for MCDs, beyond systemic mastocytosis,[57] will provide treatment guidelines and information[51] and further facilitate access to appropriate medications, including compounding if necessary, to avoid sensitivities to active or excipient ingredients. Patient advocacy groups can mediate among all players, including suppliers, to ensure continued access to necessary and trigger-free medicines. Research into repurposing medicines currently used off-label for MCD management (eg, omalizumab, cromolyn sodium, ketotifen)[56,60-63] is critical for formulary inclusion and access.

Patients desire curative treatments for MCDs. Mechanisms behind clonal MCDs are better understood, facilitating the development of targeted treatments (eg, tyrosine kinase inhibitors),[6,58] but curative treatments remain elusive. Possible future therapeutic options may include sialic acid—binding immunoglobulin-like lectin-8 and Mas-related G protein—coupled receptor-X2 receptor therapy.[64,65] Substantial commitment is required to elucidate MCAS etiologies. Initial advances identified important bone marrow changes in patients with MCAS and elevated tryptase (may correlate with presence of HαT).[66] To continue expanding the comprehension of MCAS, large-scale multicenter studies are needed.

Pharmaceutical companies will more likely address a disease when provided access to patients, easily identified end points, preexisting QoL data, and active support from PAGs and key physicians. Patient advocacy groups can facilitate connections and provide support and information to encourage rare disease drug development, approvals, and partnerships. Physicians and PAGs must help regulators understand unmet patient needs, potential outcome measures, and tolerable drug side effects.

Patient registries can address many issues identified here (see the Discussion section of the Appendix). The ECNM registry has dramatically improved understanding of mastocytosis,[67] but it does not include patient-reported outcomes or QoL data. An ideal registry would be globally networked, include mastocytosis and MCAS with comorbidities and HαT, be interoperable with existing registries, incorporate patient-reported outcomes and QoL data, and protect privacy.

Mast cell activation syndrome diagnosis: issues

Many MCAS issues result from a lack of WHO-approved MCAS diagnostic criteria (Figure 2). In numerous countries, MCAS is not yet recognized. Consensus diagnostic criteria, proposed in 2012, have since been revised.[1,8] In addition, alternate criteria were proposed,[68] confusing physicians and patients and preventing MCAS recognition, accurate diagnosis, and SoC development.[17,38] Health care professional impressions of MCAS are sometimes negative, further hindering access to care. Patient community discord also exists regarding valid MCAS diagnosis, and some patients are not open to accepting an alternative diagnosis. Health care professionals may be unfamiliar with MCAS screening, resulting in a missed diagnosis. There is limited access to the few validated diagnostic tests, especially during an acute reaction. Patients with MCAS are classified together regardless of symptoms, anaphylaxis frequency or presentation, triggers, medication response, mediator elevation, and comorbidities or HαT. Patients who fail to demonstrate an MC mediator rise, but meet the other MCAS criteria,[1,8] exist in diagnostic limbo.[14,69] Patient advocacy groups also support those patients. In some centers, care continues under a provisional diagnosis and/or using current ICD-10-CM codes.

Mast cell activation syndrome diagnosis: possible solutions

To improve MCAS diagnosis, essential factors are the acceptance of criteria and associated international ICD codes by the WHO,[1] SoC written by HCPs, a comprehensive approach to patient evaluation, and better characterization of MCAS. The development of new diagnostic tests and MC activation tests that are accessible during a reaction is imperative.

Recently, new classifications for patients not meeting all MCAS criteria were proposed by the consensus group.[1] These relate to ICD-10-CM codes used in the United States and other countries (MC activation, unspecified [D89.40], and other MCAD [D89.49]) and pave the way to improving diagnosis and care. Research should also target the role basophils may have in anaphylaxis and what seems to present as MC activation reactions.

Patients and society: issues

Patients were concerned about society's poor understanding of MCDs (particularly symptom onset unpredictability and trigger validity and variability) (Figure 3) and maintaining relationships.[17,29] Many mastocytosis or MCAS symptoms are invisible (brain fog, gastrointestinal issues, anxiety and depression, fatigue, etc) but may lead to social isolation.[16,17] Visible skin lesions might generate further stigmatization, which is compounded for children and teenagers who are already challenged by normal development.[17,70]

Children cannot always advocate for themselves and are often in school or childcare environments without control over patient-reported, parent-reported, or physician-confirmed triggers (temperature, odors, foods, exertion, friction, stress, fatigue, and chemicals).[19,29,34] They may require access to medication, including epinephrine, and may experience more illness-related absences. Many school-based challenges may continue into higher education and work environments.[34] Nevertheless, many people with MCD develop strategies to complete their education and thrive professionally.

Patients and society: possible solutions

Educating patients and society about MCDs to increase awareness, promote inclusion, and prevent bullying could improve patient QoL.[34] Research to validate patient-reported environmental triggers and education about their impact are needed to advocate for trigger-reduced environments. See Appendix for a list of HCP/PAG web resources and Box E2 for information commonly requested by patients.[34]

Inclusive educational environments are critical for children with MCDs, as for all children, but with the addition of personalized plans incorporating necessary HCP-recommended accommodations (see the Discussion section of the Appendix and citation for details).[34] Patient advocacy groups should advocate for schools to have nurse or medical assistants and readily available injectable epinephrine, if not already in place. School staff and volunteers should be trained to recognize anaphylaxis and follow the child's action plan. In higher education and workplaces, HCP-recommended accommodations may be needed (see the Discussion section of the Appendix and citation for details).[34] Coordination of the overall management of pediatric patients relies on strong partnerships among

physicians, school systems, and parents. Some excellent programs have been developed to train school staff to recognize and treat anaphylaxis (eg, Code Ana).[71] In addition, some PAGs, with the support of physician networks, can advocate to develop or improve disability benefits for patients with episodic, chronic, or rare illnesses.[34]

The Awareness Day Committee and PAGs promote the patient voice through support, advocacy, and education. Establishment of PAGs into other countries will strengthen patient support. Funding is critical, especially in lower-income countries. Sharing resources for developing initiatives is essential for network expansion, including a mentoring program for start-up PAGs.

Actors with a role in addressing patient-reported unmet needs

Actions to resolve issues reported by patients with MCDs require involving multiple key players (Figure 4). Health care professionals and PAGs are players driving solutions for all issues. Health care professionals have important roles in health-related issues and can have supporting roles in moving forward issues such as governmental and societal concerns. Education of HCPs, clarification of MCAS etiology, and collaboration in a multicenter study to validate patient-reported triggers and symptom diversity are clear areas for immediate actions by HCPs. Support for school or work accommodations and partnership with PAGs regarding patient and societal education are opportunities in which physicians can help meet needs.

CONCLUSIONS

This OIS project aims to expand understanding of the needs of patients, families, and caregivers affected by mastocytosis and MCAS, improve QoL, and encourage global communication among key actors. Identified issues require multifaceted, national and international, collaborative approaches, especially for HCP education, the establishment of new CoE/RC, WHO acceptance of MCAS diagnostic criteria, MCD-focused research, and patient registries. Positive outcomes should result from rare disease partnerships.[72-74] Funding to support activities that address unmet needs is critical. Future projects must explore equity in accessing care for MCDs, especially in low-resource settings, and the concerns of individual categories of patients.

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