Pyatilova et al. World Allergy Organization Journal (2023) 16:100838
http://doi.org/10.1016/j.waojou.2023.100838

WORLD ALLERGY ORGANIZATION JOURNAL

Open Access

The diagnostic workup for systemic mastocytosis differs from consensus recommendations: Results of a worldwide survey

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ABSTRACT

Objective: Mastocytosis is a complex disorder affecting various organs. The diagnostic workup can be challenging and requires a multidisciplinary approach including the use of uncommon tests. To assess mastocytosis management around the globe, we conducted the first worldwide online survey for physicians.

Methods: A 21-item questionnaire was sent out to the members of the World Allergy Organization (WAO), the Global Allergy and Asthma European Network (GA^{2}LEN), the Urticaria (UCARE) and Angioedema (ACARE) Centers of Reference and Excellence, the German Society of Allergology and Clinical Immunology (DGAKI), and the European Mast Cell and Basophil Research Network (EMBRN) in April–June 2021.

Results: Across 628 respondents from 79 countries 87.7% and 9.7% of physicians were allergists/clinical immunologists and/or dermatologists. Participating physicians were from all regions of the world (Europe, EU: 41.6%; North America, NA: 24.8%; Latin America, LA: 14.5%; Asia-Pacific, AP: 12.6%; and Africa/Middle East, AME: 6.5%). Only 2.2% of respondents worked at Specialized Mastocytosis Centers (SMCs) in North America or European Union. Physicians reported caring for 4 patients with mastocytosis per year, with higher numbers in European Union and Asia Pacific (5/year) compared to Latin America (2/year). Dermatologists and physicians who work at SMCs reported higher patient numbers (15/year and 80/year, respectively). Suspicion of mastocytosis in the allergology and dermatology community is commonly driven by anaphylaxis (82.9%), mastocytosis skin lesions (82.1%), or elevated tryptase levels (76.6%). Osteoporosis and gastrointestinal symptoms less often prompted suspicion of mastocytosis (21.4% and 49.9%, respectively). World Health Organisation (WHO)-diagnostic criteria and classification, regardless of the region, are only used by about 50% of physicians, with higher rates for SMCs (83.3%). Serum tryptase, bone marrow biopsy, and *KIT* D816V mutation analysis are included in the diagnostic workup by 90.9%, 61.5%, and 58.4% of physicians, respectively. The biggest challenges for the management

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http://doi.org/10.1016/j.waojou.2023.100838
Received 18 August 2023; Received in revised from 4 October 2023; Accepted 17 October 2023
Online publication date xxx

of mastocytosis are the lack of more effective treatment options (51.1%), missing multidisciplinary networks (47.1%), and the lack of experience of specialists from other disciplines (39.0%).

Conclusions: The diagnostic workup for mastocytosis differs from consensus recommendations and varies between regions. This may be improved by establishing active multidisciplinary networks, increasing access to diagnostic procedures, consistently applying WHO criteria, and developing new Mastocytosis Centers of Reference and Excellence.

Keywords: Mastocytosis, Management, Challenges, Worldwide, Survey

INTRODUCTION

Mastocytosis is a rare and heterogeneous disorder characterized by an accumulation of neoplastic mast cells affecting the skin, bone marrow (BM), musculoskeletal system, gastrointestinal tract, and other organs.[1–3] The diagnostic workup for mastocytosis requires a multidisciplinary approach in adult patients.[4] According to the 2016 World Health Organisation (WHO) classification, mastocytosis can manifest as cutaneous mastocytosis (CM), non-advanced systemic mastocytosis (non-AdvSM), ie, indolent SM (ISM) and smoldering SM (SSM), and advanced SM (AdvSM), ie, SM with an associated hematologic neoplasm (SM-AHN), aggressive SM (ASM), and mast cell leukemia (MCL).[2,3,5] Most adult patients have ISM, which is driven by the *KIT* D816V mutation in >90 % of cases.[6] The prevalence of SM is increasing, from around 10 in 100 000 inhabitants 10 years ago to more than 20 in 100 000,[7–9] in part since new sensitive diagnostic approaches are being applied and because of growing awareness raised by scientific communities, such as the European Competence Network on Mastocytosis (ECNM) and the American Initiative in Mast Cell Diseases (AIM).

The diagnostic criteria for SM, including multifocal dense mast cell infiltrates and altered mast cell morphology, are most reliably detected in the bone marrow (BM). The presence of the *KIT* D816V mutation and elevated serum basal tryptase levels (sBT) of >20 ng/mL can be detected in the peripheral blood with a high sensitivity and support the suspicion of SM.[2] The definition of SM subtypes requires the correct interpretation of a number of diagnostic measures, including sBT levels, extended molecular mutation profiles, mast cell burden in BM biopsy and aspirate, signs of myeloproliferation/dysplasia, the presence of discrete cytopenia/cytosis, organomegaly (B-findings) as well as signs of organ damage (C-findings), ie, prominent cytopenia, malabsorption, weight loss, and large osteolytic bone lesions, ascites, and hypersplenism.[2,3,5] SM criteria have been modified in the updated 2022 WHO classification, introducing new diagnostic criteria, ie, CD30 expression, *KIT* mutations in other domains, *KIT* D816V allele burden ≥10 %, adjustment of sBT to alpha-tryptase gene copy number, and new SM subtype, ie, bone marrow mastocytosis (BMM).[10]

Currently, the approaches to diagnosing mastocytosis used by physicians in everyday practice worldwide are poorly investigated. Over the past years, a few survey studies in the United States have provided data on disease impact and diagnostic measures from a patient perspective.[11–13] In 2022, another patient-designed survey was distributed in 12 regions (Austria, Germany, France, Italy, Spain, the United Kingdom, Mexico, the Netherlands, Romania, Poland, the United States, and Australasia).[14] More recently, a survey study assessed mastocytosis management among allergists (51 %) and hematologists (49 %), but only physicians with experience in mastocytosis management from a single country were involved.[15]

Globally, the management of mastocytosis can vary due to differences in national guidelines, access to medical and technical equipment and resources, and levels of awareness, expertise, and experience. In this project, we aimed to identify the current challenges in mastocytosis management faced by physicians worldwide in their everyday

practice. To do so, we conducted an online survey for specialists to assess the visibility, capacity, awareness, expertise and availability of basic diagnostic procedures and the existence and access to functional interdisciplinary networks.

MATERIALS AND METHODS

Development of a questionnaire and distribution

An initial questionnaire was developed and pilot-tested in physicians involved in the care of mastocytosis. Next, 21 questions (Suppl. Fig. 1) were selected and approved by the Global Allergy and Asthma European Network (GA^2LEN), Urticaria Network (UNEV), the World Allergy Organization (WAO) Skin Allergy Committee and the WAO Leadership and Board of Directors. Finally, the online survey platform was established, and the questionnaire was sent out in April 2021 to all members of WAO. Simultaneously, the link to the survey was distributed among members of GA^2LEN, the Urticaria (UCARE) and Angioedema (ACARE) Centers of Reference and Excellence, the German Society of Allergology and Clinical Immunology (DGAKI) and the European Mast Cell and Basophil Research Network (EMBRN). The survey was closed in June 2021.

Data evaluation

All physicians provided data on their specialty and work environment. Three questionnaires were excluded from the final analyses because of inconsistent data, ie, contradictive data or $\geq$1000 patients with mastocytosis mentioned to be seen per year. Questionnaires with partially missing information were included in the analysis.

Statistical analysis

The Statistical Package for the Social Science (IBM SPSS version 29.0; IBM Corp. 2022, New York, NY), R (R Foundation for Statistical Computing) and GraphPad Prism version 8.0 (GraphPad Software, San Diego, California USA) were used for the analysis. Data were presented as median (interquartile range). Statistically significant differences between groups were calculated using the Kruskal-Wallis test with the Bonferroni correction for continuous variables and the chi-square test for categorical variables. $P < 0.05$ was considered statistically significant.

RESULTS

Demographic characteristics, specialty, and work environment of the respondents

Across 628 physicians from 79 countries (Suppl. Table 1, Fig. 1), allergy/clinical immunology (87.7%), pediatrics (15.1%), and dermatology (9.7%) were the most represented specialties, and 20% had more than 1 specialty, mostly allergy/clinical immunology and pediatrics or dermatology (Table 1). Most physicians were from Europe (EU: 41.6 %), followed by North

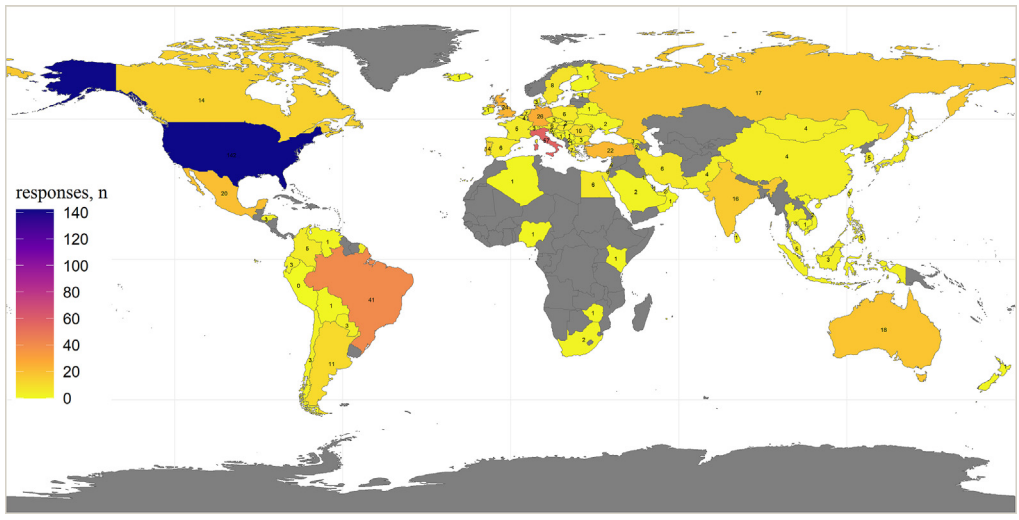


Fig. 1 Number of participating physicians per country (n = 628). Countries where physicians have not provided responses are shown in grey

Parameter, n (%)	Worldwide	Regions				
		NA	LA	EU	AME	AP
Specialty[a]	*n = 628 (100)*	*n = 156 (24.8)*	*n = 91 (14.5)*	*n = 261 (41.6)*	*n = 41 (6.5)*	*n = 79 (12.6)*
Allergy/Immunology	551 (87.7)	151 (96.8)	88 (96.7)	220 (84.3)	34 (82.9)	58 (73.4)
Pediatrics	95 (15.1)	8 (5.1)	26 (28.6)	34 (13.0)	13 (28.9)	14 (18.7)
Dermatology	61 (9.7)	2 (1.3)	2 (2.2)	40 (15.3)	2 (4.9)	15 (19.0)
General Practice	11 (1.8)	2 (1.3)	0 (0.0)	2 (0.8)	3 (6.7)	4 (5.3)
Pulmonology	11 (1.8)	0 (0.0)	1 (1.1)	5 (1.9)	2 (4.4)	3 (4.0)
Internal Medicine	10 (1.6)	0 (0.0)	1 (1.1)	7 (2.7)	1 (2.2)	1 (1.3)
Hematology	6 (1.0)	3 (1.9)	0 (0.0)	3 (1.1)	0 (0.0)	0 (0.0)
Otolaryngologist	6 (1.0)	0 (0.0)	0 (0.0)	2 (0.8)	1 (2.2)	3 (4.0)
>1 specialty	123 (20.0)	11 (7.0)	27 (29.7)	52 (19.9)	13 (31.7)	20 (25.3)
Work environment[a]						
Private Practice	276 (43.9)	84 (53.2)	74 (7.7)	72 (27.6)	15 (33.3)	31 (41.3)
Hospital	268 (42.7)	29 (18.4)	41 (45.1)	130 (49.8)	23 (56.1)	45 (57.0)
University Clinic	228 (36.3)	53 (33.5)	27 (29.7)	108 (41.4)	17 (41.5)	23 (29.1)
SMCs	14 (2.2)	2 (1.3)	0 (0.0)	12 (4.6)	0 (0.0)	0 (0.0)
Practice						
Years, median (IQR)	18 (10–30)	20 (10–31)	20 (8–30)	16 (9–25)	15 (7–23)	20 (10–30)
Mastocytosis population	***n = 604***	***n = 150***	***n = 86***	***n = 253***	***n = 40***	***n = 75***
Both children and adults	258 (42.7)	89 (59.3)	51 (59.3)	83 (32.8)	14 (35.0)	21 (28.0)
Adults only	225 (37.3)	47 (31.1)	13 (15.1)	124 (49.0)	11 (27.5)	30 (40.0)
Children only	121 (20.0)	14 (9.3)	22 (25.6)	46 (18.2)	15 (37.5)	24 (32.0)

Table 1. General characteristics of the physicians who participated in the survey *Abbreviations: AME, Africa/Middle East; AP, Asia-Pacific; EU, Europe; IQR, interquartile range; LA, Latin America; NA, North America; SMCs, specialized mastocytosis centers; n, number.* [a]*Several options could be applied.*

America (NA: 24.8%), and Latin America (LA: 14.5%). Detailed information on the numbers of participating physicians per region are provided in Suppl. Table 1.

Most physicians worked in a private practice (43.9%), hospital (42.7%), or university clinic (36.3%). Only 14 physicians (2.2%) worked at specialized mastocytosis centers (SMCs), in North America and Europe. On average, physicians had 18 years of work experience; they cared for adults and children with mastocytosis (42.7%), adult patients only (37.3%), or treated children with mastocytosis (20%).

The demographic characteristics, specialties, work environments, and patient populations of respondents are summarized in Table 1. The results are based on the analysis of physicians who treat adult patients with mastocytosis.

The number of patients with mastocytosis seen by physicians

Physicians, on average, reported caring for 4 patients with mastocytosis per year (Table 2), with

Parameter		World-wide	Regions						
			NA (1)	LA (2)	EU (3)	AME (4)	AP (5)	p-value[b]	Pairwise[b]
		n = 479	n = 134	n = 64	n = 207	n = 25	n = 49		
Patients /year, n[a]	all	4 (1–10)	4 (2–8)	2 (1–2)	5 (2–20)	3 (1–5)	5 (1–10)	<0.001	1,2 vs. 3; 2 vs 5
	new	1 (1–3)	1 (1–2)	1 (0–1)	2 (1–5)	1 (1–2)	2 (1–4)	<0.001	1 vs. 2,3; 2 vs. 3,5
		n = 409	*n = 128*	*n = 61*	*n = 163*	*n = 22*	*n = 35*		
Patients /year seen by A, n[a]	all	3 (1–10)	4 (2–8)	2 (1–3)	5 (2–15)	4 (2–5)	6 (1–12)	<0.001	2 vs. 1,3,5
	new	1 (1–3)	1 (1–2)	1 (0–1)	2 (1–4)	1 (1–2)	2 (1–5)	<0.001	2 vs. 1,3,4,5
		n = 49	*n = 1*	*n = 2*	*n = 37*	*n = 0*	*n = 9*		
Patients /year seen by D, n[a]	all	15 (5–48)	2[c]	1,2[c]	20 (10–50)	-	5 (3–9)	0.003	3 vs. 5
	new	4 (2–9)	1[c]	1,2[c]	5 (3–15)	-	2 (1–2)	0.003	3 vs. 5
		n = 482	*n = 136*	*n = 64*	*n = 207*	*n = 25*	*n = 50*		
>10 patients/y, n (%)		108 (22)	22 (16)	1 (2)	72 (35)	3 (12)	10 (20)	<0.001	2 vs. 1,3,5
		n = 396	*n = 112*	*n = 49*	*n = 176*	*n = 19*	*n = 40*		
"not sure" how many patients have SM, n (%)		218 (55)	64 (57)	36 (74)	88 (50)	11 (58)	19 (48)	0.046	2 vs. 3
		n = 173	*n = 48*	*n = 12*	*n = 87*	*n = 7*	*n = 19*		
Confirmed SM, %[a]		50 (10–90)	80 (10–99)	23 (1–50)	50 (18–90)	80 (1–80)	30 (0–80)	0.031	ns

Table 2. Number of patients with mastocytosis seen by physicians per year. *Abbreviations: A, allergist/immunologist without dermatology as a side specialty; AME, Africa/Middle East; AP, Asia-Pacific; D, dermatologist with and without allergology as a side specialty; EU, Europe; IQR, interquartile range; LA, Latin America; NA, North America; n, number; ns, non-significant.* [a]*The number of patients and percentage of patients with confirmed SM are shown as median (IQR).* [b]*Only statistically significant comparisons are shown. The 'p-value' column refers to the difference in proportions between the regions. In the 'pairwise' column, statistically significant differences between pairs of regions, coded as NA (1), LA (2), AME (3), AME (4) and A (5), are included.* [c]*Distinct answers are shown, as only 1–2 responses were present.*

higher numbers in Europe and Asia-Pacific (AP: 5/year) compared to Latin America (2/year; $p < 0.001$). Every third EU physician (35 %) saw >10 patients with mastocytosis per year, compared with 2%, 12%, 16%, and 20% of physicians in Latin America, Africa and Middle East (AME), North America, and Asia Pacific, respectively. Dermatologists vs allergists, and physicians working at SMCs reported high patient numbers (median/range: 15/5–48 per year and 80/18–300, respectively; Table 2, Suppl. Table 2).

Only 1 new patient per physician per year was seen worldwide, with the highest rates in Europe and Asia Pacific (2/year), dermatology (4/year) and SMCs (10/year; Table 2, Suppl. Table 2).

Patients with mastocytosis are referred to and from other specialists

More than two-thirds of physicians (72.3%) reported referrals from other specialists, with the rate between 16.7% and 45.4% in Latin America and Europe, respectively. Referrals were more frequently received from dermatologists, general practitioners, and hematologists (56.7%, 45.3%, and 36.1%, respectively; Suppl. Table 3).

Physicians (76.6%) also referred patients to other specialists, varying from 60.9% in Latin America to 84.1% in Europe. Patients were referred to hematologists (76.5%), dermatologists (30.5%), and allergists/clinical immunologists (23.0%). The most common reason for referral was "diagnostic workup" (74.3%) and "treatment optimization" (37.8%; Suppl. Table 3). Across all physicians, 24.6% were referred to an SMC, with the highest rates in Europe (33.3%) and NA (27.8%) compared to Latin America (5.1%) and Asia Pacific (3.2%; Suppl. Table 3).

A suspicion of mastocytosis is mostly driven by anaphylaxis, skin lesions, and elevated tryptase levels

Most physicians reported that their suspicion of mastocytosis in adults is driven by anaphylaxis, mastocytosis skin lesions, or elevated tryptase levels (82.9%, 82.1%, and 76.6%, respectively, Fig. 2). However, reports on anaphylaxis varied from 67.3% to 88.6% between regions. Osteoporosis and gastrointestinal symptoms prompted suspicion of mastocytosis less frequently (21.4% and 49.9%, respectively; Fig. 2).

The diagnostic workup for systemic mastocytosis differs from the consensus recommendations and varies between regions

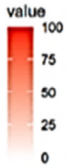
The WHO diagnostic criteria and WHO classification for SM were used by only 57.7% and 45.3% of physicians, respectively, with higher rates in SMC physicians (83.3% for both), compared to Latin America (50.0% and 29.2%, respectively; Fig. 2, Suppl. Table 2). Assessment of B- and C-findings was reported by 12.7% of respondents (EU: 18.2%, SMC physicians: 66.7%), and sBT was included in the diagnostic workup by 90.9% of physicians (North America: 97.3%, Europe: 95.5%, SMC physicians: 100%). BM biopsy, the primary procedure for SM diagnosis, was applied by 61.5% of physicians (NA: 73.2%, AME: 70.0%, SMC physicians: 91.7%). *KIT* D816V mutation analysis of peripheral blood (PB) was used by 58.4% of physicians (NA: 85.7%, EU: 54.0%, SMC physicians: 100%). Other diagnostic tests, such as complete blood counts and bone density scans, were implemented by 79.8% and 45.1% of physicians, respectively (Fig. 2).

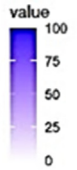
Systemic mastocytosis is confirmed in every second patient

Respondents reported that, on average, the diagnosis of SM is confirmed in about half of adult patients with mastocytosis. Despite being recommended by expert consortia, a diagnostic workup aiming to evaluate systemic involvement in patients with clinical evidence of mastocytosis was not performed in many patients. However, more than half of the respondents did not provide an answer on the percentage of confirmed SM among their patients with mastocytosis. Interestingly, the percentage of confirmed SM varied from 23% to 80% between the regions, being 80% in North America and Africa/Middle East, and 23–30% in Latin America and Asia Pacific regions (Table 2).

Challenges faced by physicians

The most common challenges in the management of mastocytosis, as reported by 51.1%, 47.1%, and 39.0% of physicians, respectively, were the lack of more effective treatment options, missing or a lack of multidisciplinary networks, and





	Parameter, n (%)	WW	Comparison of regions (groups 1-5)						
			NA (1)	LA (2)	EU (3)	AME (4)	AP (5)	*P*	Pairwise[a]
Signs/symptoms		*n=397*	*n=112*	*n=49*	*n=176*	*n=19*	*n=41*		
	Anaphylaxis	329 (82.9)	98 (87.5)	33 (67.3)	156 (88.6)	14 (73.7)	28 (68.3)	<0.001	1,3 vs2; 3 v s5
	MIS	326 (82.1)	85 (75.9)	42 (85.7)	146 (83.0)	18 (94.7)	35 (85.4)	ns	ns
	Elevated sBT	304 (76.6)	100 (89.3)	20 (40.8)	145 (82.4)	15 (78.9)	24 (58.5)	<0.001	1,3 vs 2,5; 2 vs 4
	GI symptoms	198 (49.9)	74 (66.1)	18 (36.7)	74 (42.0)	11 (57.9)	21 (51.2)	0.001	1 vs 2,3
	Osteoporosis	85 (21.4)	17 (15.2)	6 (12.2)	50 (28.4)	4 (21.1)	8 (19.5)	0.037	ns
Criteria to rely on when diagnose and/or classify SM		*n=395*	*n=112*	*n=48*	*n=176*	*n=19*	*n=40*		
	WHO-criteria	228 (57.7)	75 (67.0)	24 (50.0)	95 (54.0)	11 (57.9)	23 (57.5)	ns	ns
	WHO-classification	179 (45.3)	53 (47.3)	14 (29.2)	84 (47.7)	8 (42.1)	20 (50.0)	ns	ns
	B-/C-findings	50 (12.7)	10 (8.9)	2 (4.2)	32 (18.2)	2 (10.5)	4 (10.0)	0.045	ns
		n=397	*n=112*	*n=49*	*n=176*	*n=20*	*n=40*		
	sBT	361 (90.9)	109 (97.3)	35 (71.4)	168 (95.5)	17 (85.0)	32 (80.0)	<0.001	1,3 vs 2,5
	BM biopsy	244 (61.5)	82 (73.2)	25 (51.0)	101 (57.4)	14 (70.0)	22 (55.0)	0.023	ns
	KIT D816V in PB	232 (58.4)	96 (85.7)	14 (28.6)	95 (54.0)	9 (45.0)	18 (45.0)	<0.001	1 vs2,3,4,5; 3 vs 2
	KIT D816V in BM	170 (42.8)	61 (54.5)	10 (20.0)	76 (43.2)	8 (40.0)	15 (37.5)	0.002	1,3vs2
	Blood count	317 (79.8)	104 (92.9)	32 (65.3)	140 (79.5)	15 (77.3)	26 (65.0)	<0.001	1vs2,3,5
	Bone density scan	179 (45.1)	37 (33.0)	19 (38.8)	91 (51.7)	11 (55.0)	21 (52.5)	0.016	3vs1

Fig. 2 Signs/symptoms leading to the suspicion of mastocytosis, criteria physicians rely on when diagnosing and/or classifying SM, and tests included in the diagnostic workup for SM. [a] Only statistically significant comparisons are shown. The "p-value" column refers to the differences in proportions between the regions. In the "pairwise" column, statistically significant differences between pairs of regions, coded as NA (1), LA (2), AME (3), AME (4), and A (5) are included; Abbreviations: AME, Africa/Middle East; AP, Asia-Pacific; BM, bone marrow; EU, Europe; GI, Gastrointestinal; LA, Latin America; MIS, Mastocytosis in the skin; ns, non-significant; NA, North America; PB, peripheral blood; sBT, serum baseline tryptase; SM, systemic mastocytosis; WHO, World Health Organisation; WW, worldwide

the lack of experience of specialists from other disciplines (Table 3). About every third physician reported a lack of access to diagnostic procedures or experience (33.9% and 29.1%, respectively). High treatment costs and absence of treatment choices were reported by 19.0% and 11.9% of physicians, respectively (Table 3).

SMC physicians most commonly see "lack of experience by specialists from other disciplines" and "lack of more effective treatment options" as their biggest challenges (75.0% and 66.7%, respectively).

DISCUSSION

This is global survey among physicians, primarily allergologists, that identified differences in the diagnostic workup and challenges faced by physicians treating adult patients with mastocytosis. Our findings reveal multiple major unmet needs in managing mastocytosis patients around the globe.

It has previously been shown that adult patients with SM are initially diagnosed by allergists/immunologists (31–43%), dermatologists (23–94%), hematologist (21–26%), and rarely, gastroenterologists (5–10%).[11,13,15,16] Allergists/immunologists also see most patients with indolent forms of mastocytosis.[15] The median number of patients with mastocytosis reported to be seen by physicians in this survey was low, ie, 4 patients per year in total and 1 new patient per year. This is in line with a survey among 111 US physicians who, during their average 14-year practice treated about 20 patients with mastocytosis.[15] In

Parameter, n (%)	World-wide *n = 395*	Regions						
		NA (1) *n = 112*	LA (2) *n = 48*	EU (3) *n = 176*	AME (4) *n = 19*	AP (5) *n = 40*	*p*-value[a]	Pairwise[a]
Lack of more effective treatment options	202 (51.1)	63 (56.3)	15 (31.3)	88 (50.0)	11 (57.9)	25 (62.5)	0.024	1 vs 2
Multidisciplinary network is missing/not active	186 (47.1)	55 (49.1)	26 (54.2)	80 (45.5)	9 (47.4)	16 (40.0)	ns	ns
Specialists from other disciplines lack experience	154 (39.0)	52 (46.4)	18 (37.5)	61 (34.7)	7 (36.8)	16 (40.0)	ns	ns
Not all diagnostic procedures are accessible	134 (33.9)	30 (26.8)	23 (47.9)	57 (32.4)	8 (42.1)	16 (40.0)	ns	ns
I feel not being experienced enough	115 (29.1)	35 (31.3)	17 (35.4)	50 (28.4)	5 (26.3)	8 (20.0)	ns	ns
Treatment costs are too high for my patients	75 (19.0)	22 (19.6)	16 (33.3)	21 (11.9)	6 (31.6)	10 (25.0)	0.005	2 vs 3
Treatment of choice is not available in my country	47 (11.9)	3 (2.7)	12 (25.0)	20 (11.4)	3 (15.8)	9 (22.5)	<0.001	1 vs 2,5

Table 3. Challenges faced by physicians of patients with mastocytosis *Abbreviations: AME, Africa/Middle East; AP, Asia-Pacific; EU, Europe; LA, Latin America; NA, North America; n, number; ns, non-significant. [a]Only statistically significant comparisons are shown. The 'p-value' column refers to the difference in proportions between the regions. In the 'pairwise' column, statistically significant differences between pairs of regions, coded as NA (1), LA (2), AME (3), AME (4) and A (5) are included.*

our study, we received responses mostly from allergists. Despite our global outreach, the responses by dermatologists were limited to Europe and Asia Pacific as well as physicians working in a SMC to 7 countries (the United States, Greece, Germany, Italy, Belgium, the Netherlands, and Denmark). Dermatologists and SMC physicians who participated in our study, cared for a larger number of patients with mastocytosis compared with allergists (15 and 80 vs 3, respectively). The reasons for this could include previously reported more prevalent skin involvement (>80%) compared to anaphylaxis (20–56%).[17-21] The mastocytosis networks inEurope and the United States are well recognized, with more than 25 established SMCs in Europe and about 10 SMCs in the United States.[22,23] However, other regions still lack recognized SMCs. More than half of physicians receive referrals from dermatologists, indicating the role of dermatologists as "gatekeepers" in the diagnosis of mastocytosis.

Our survey shows that most physicians referred patients to hematologists for a diagnostic workup. Treatment optimization and initiation were other common reasons for referrals. Every third physician from North America and the Europe referred patients to an SMC. This points to the complexity of the diagnostic workup in mastocytosis and the need for its optimization, as well as access to better treatment options and multidisciplinary networks.

The diagnostic workup for SM was commonly incomplete and varied among the regions and when comparing non-mastocytosis specialists to SMCs. Only every second physician applied WHO criteria and WHO classification for SM. This is in line with the results of a patient survey showing that mastocytosis was not diagnosed in accordance with recommendations and consensus criteria in up to 60% of cases.[12]

According to the WHO standards BM investigation is required in each patient. Only half of the respondents considered BM investigation in the diagnostic workup of SM. The low adherence to performing BM biopsies might be explained by several reasons, including limited access to a multidisciplinary network, shortage of resources, an under-recognized need to perform a BM biopsy in every patient, or lack of experience. Of note, sBT is included in the diagnostic workup by 90.9% of physicians worldwide but is less common in Latin America. *KIT* D816V mutation analysis in PB is the least frequently used diagnostic test, applied by 20.0–85.7% of physicians, depending on the region. This may be explained by limited access, low awareness and/or high test costs. Access to the test in the United States was previously reported by the Touchstone study.[15] However, Boggs and coauthors showed that *KIT* D816V mutation could be challenging, highlighting discordant results when using different methods.[24]

Based on this physician survey, the diagnosis of systemic mastocytosis is only confirmed in every second patient. This outcome emphasizes that patients may have been lost to follow-up or were not consistently subjected to recommended diagnostic procedures.[25] Identifying possible reasons for this inconsistency and low adherence to the use of recommended diagnostic measures in mastocytosis is of particular importance since novel more effective treatment options are currently becoming available.[26–30] As of yet, criteria for prognosis with the use of minimally invasive procedures in patients who have not undergone BM investigations are missing.

Finally, our study shows that the lack of more effective treatment options and missing multidisciplinary networks were perceived as the biggest challenges in the management of patients with mastocytosis. This is in line with other studies, which revealed poor control of symptoms despite the use of 3 or more medications.[13,16] The lack of experience of specialists from other disciplines, previously identified in a study among 12 countries, was also commonly mentioned in our study on a global level.[14] Our results support another study where some patients were diagnosed with SM only after re-examination of BM by an expert hemathopathologist, proposing a need for centralized BM sample evaluations.[24] Lastly, not having all diagnostic procedures accessible is another important challenge recognized in our study. This may explain the diagnostic delay, as stated by patients in other studies.[13,16,31]

Limitations

One limitation of this study is its primary focus on the community of allergists/immunologists and the underrepresentation of hematologists, which could have influenced the results of our analysis. Similar surveys among physicians from other specialties are needed to broaden the insight into the entire expert community that provides care to patients with mastocytosis. However, we believe that data provided by such a large cohort of allergiologists is of great importance to understand the current unmet needs and challenges of healthcare providers around the globe. Another limitation is that physicians without any experience in managing patients with mastocytosis may have not responded to this survey.

Conclusions and unmet needs

Our survey results identified worldwide diagnostic approaches, access to and availability of resources required for state-of-the-art management of patients with mastocytosis. First, diagnostic workup for mastocytosis is commonly incomplete. Our study showed that the WHO criteria and WHO classification are being used only by half of physicians. Better access to diagnostic tests and adjustment of criteria and classification may support standardization in the diagnosis of mastocytosis and enable physicians to follow the recommended guidelines. Secondly, additional criteria for patient prognosis within the group of non-advanced patients with mastocytosis to identify those with the highest need for complete diagnostic workup, including BM investigation, are needed. Furthermore, many regions lack centers of reference and excellence, thus not reaching the aspired level of awareness, doctors' experience, and patient management. Finally, access to better treatment options for patients with mastocytosis is highly desirable. Future activities should address reported challenges in managing mastocytosis in different regions and specialties.

Abbreviations

ACARE, Angioedema Centers of Reference and Excellence; AdvSM, Advanced forms of SM; AIM, American Initiative in Mast Cell Diseases; ASM, Aggressive systemic mastocytosis; AME, Africa/Middle East; AP, Asia-Pacific; BM, Bone marrow; BMM, Bone marrow mastocytosis; CM, Cutaneous mastocytosis; DGAKI, German Society of Allergology and Clinical Immunology; ECNM, European Competence Network on Mastocytosis; EMBRN, European Mast Cell and Basophil Research Network; EU, Europe; GA^{2}LEN, Global Allergy and Asthma European Network; ISM, Indolent systemic mastocytosis; LA, Latin America; MCL, Mast cell leukemia; NA, North America; sBT, Serum baseline tryptase; SM, Systemic mastocytosis; SM-AHN, Systemic mastocytosis with an associated hematologic neoplasm; SMCs, Specialized mastocytosis centers; SSM, Smoldering systemic mastocytosis; UCARE, Urticaria Centers of Reference and Excellence; UNEV, Urticaria Network e.V.; WAO, World Allergy Organization; WHO, World Health Organization; WW, Worldwide.

Acknowledgment of funding

This project benefitted from the support of the World Allergy Organization, GA^{2}LEN network of urticaria centers of references and excellence (UCAREs; www.ga2len-ucare.com) and Blueprint Medicines Corporation.

Disclosure of potential conflict of interest

Polina Pyatilova has no relevant conflict of interest in relation to this work.
Jonathan A. Bernstein has no relevant conflict of interest in relation to this work. Outside of it, JB was a PI and/or consultant for Blueprint Medicine and Cogent pharmaceuticals; AIM center of excellence, president AAAAI, member of JTF guideline committee.
Saša Dimitrijević and Gerard Hoehn are employees and equity holders of Blueprint Medicines Corporation.
Marcus Maurer has no relevant conflict of interest in relation to this work. Outside of it, MM is or recently was a speaker and/or advisor or received institutional research funding from Astria, Allakos, Alnylam, Amgen, Aralez, ArgenX, AstraZeneca, BioCryst, Blueprint, Celldex, Centogene, CSL Behring, Dyax, FAES, Genentech, GIInnovation, GSK, Innate Pharma, Kalvista, Kyowa Kirin, Leo Pharma, Lilly, Menarini, Moxie, Noucor, Novartis, Pfizer, Pharming, Pharvaris, Roche, Sanofi/Regeneron, Shire/Takeda, Third Harmonic Bio and UCB.
Pavel Kolkhir has no relevant conflict of interest in relation to this work. Outside of it, PK is or recently was a speaker and/or advisor for Novartis, Roche and ValenzaBio.
Frank Siebenhaar has no relevant conflict of interest in relation to this work. Outside of it, FS is or recently was a speaker and/or advisor for and/or has received research funding from Allakos, Blueprint Medicine, Celldex, Cogent, Escient, Granular, GSK, Invea, Noucor, Novartis, Moxie, Sanofi/Regeneron and Third Harmonic Bio.

Availability of data and materials

The original contributions presented in the study are included in the article/Supplemental Material. Further inquiries can be directed to the corresponding author.

Author contributions and consent

PP, FS and PK designed the study, interpreted the data and prepared the manuscript. The study was supervised by FS and PK. All coauthors critically revised and provided

substantial input to the manuscript. All authors of the manuscript have read and agreed to its content and are accountable for all aspects of the accuracy and integrity of the manuscript in accordance with the criteria of the International Committee of Medical Journal Editors (ICMJE). The manuscript is original, has not been published already, and is not under consideration by another journal. All authors agree to the terms of the Elsevier License Agreement for the World Allergy Organization Journal, and the Open Data Policy.

Ethics approval

Not applicable. The study did not involve patients.

Acknowledgements

The authors thank all the participants who completed the survey, the Board of Directors of the World Allergy Organization, the members of the GA^{2}LEN and UNEV networks and Blueprint Medicines Corporation for support of the project.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.waojou.2023.100838.

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