# Prevalence of mastocytosis and Hymenoptera venom allergy in the United States



**Charles F. Schuler IV, MD,[a,b]* Sofija Volertas, MD,[c]* Dilawar Khokhar, MD,[a] Huseyin Yuce, PhD,[d] Lu Chen, MS, MPH,[e] Onur Baser, PhD,[f] Jenny M. Montejo, MD,[g] and Cem Akin, MD[a]** *Ann Arbor, Mich; Chapel Hill, NC; New York, NY; Istanbul, Turkey; and Rochester, Minn*

**Background: Mastocytosis is a risk factor for Hymenoptera venom anaphylaxis (HVA). Current guidelines recommend measuring tryptase in patients with HVA and that those with mastocytosis pursue lifelong venom immunotherapy (VIT). Available data on HVA and mastocytosis largely derive from European single-center studies, and the prevalence of HVA with and without mastocytosis in the United States is unknown.**
**Objective: We sought to determine the prevalence of HVA and mastocytosis in the United States using an insurance claims database and evaluate the impact of mastocytosis on VIT in patients with HVA in a US cohort.**
**Methods: The IBM Watson Database, consisting of insurance claims from approximately 27 million US patients in 2018, was queried to identify patients with HVA and/or mastocytosis. Furthermore, a retrospective study of 161 patients undergoing VIT between 2015 and 2018 at the University of Michigan was conducted.**
**Results: In the IBM Watson Database, the prevalence of HVA was 167 per 100,000 (0.167%) and the prevalence of mastocytosis 10 per 100,000 (0.010%) overall and 97 per 100,000 (0.097%) among those with HVA. Mastocytosis showed a 9.7-fold increase among patients with HVA versus the general population. In the U-M cohort, 2.6% of patients with VIT had mastocytosis. Tryptase level did not correlate with venom reaction severity but was higher in patients with systemic VIT reactions.**
**Conclusions: We observed a lower US HVA prevalence than previously reported. Mastocytosis was more common in US patients with HVA, though at lower rates than previously reported. In patients with VIT there was no correlation between tryptase level and reaction severity. (J Allergy Clin Immunol 2021;148:1316-23.)**

***Key words:*** *Tryptase, venom allergy, venom immunotherapy, anaphylaxis, mastocytosis, mast cell activation syndrome, mast cell disease*

Hymenoptera venom allergy (HVA) constitutes an IgE-mediated anaphylactic reaction with a prevalence from 0.5% to 3.3% in the United States and 0.3% to 7.5% in Europe.[1,2] Patients are prescribed epinephrine as a rescue medicine and may undergo prophylactic venom immunotherapy (VIT); VIT for honeybee, vespids, and wasp reduces systemic reaction rates from 60% in untreated patients to as low as 0% to 5%.[3-5] VIT is recommended for patients with anaphylactic venom reactions.[3,5]

Previous work has shown a high prevalence among patients with HVA of up to 11.6% (or 11,600 per 100,000) with elevated serum tryptase and up to 5.5% (or 5,500 per 100,000) for clonal mast cell disease (MCD), including systemic mastocytosis (SM).[6,7] Elevated serum tryptase has been linked to severe sting reactions and reactions during VIT.[8,9] The diagnosis of SM also marks an increased risk for severe sting reactions and adverse events during VIT.[10,11] Thus, updated American Academy of Allergy, Asthma & Immunology guidelines for patients with HVA have expanded recommendations for tryptase measurement in this population.[3] However, much of the work supporting high rates of SM in patients with HVA has come from European single-center studies, many of which were also referral centers for mastocytosis and may have carried a selection bias. In addition, these studies were performed before recognition of hereditary alpha-tryptasemia.[6,7,12] A recent single-center study of 159 patients from Israel found a lower rate of tryptase elevation and MCD when compared with European data (3.8% as compared with 10%-15.9%), suggesting that geographic differences in co-occurrence of MCD and venom allergy may exist.[13] The rate of clonal MCD in the US population with HVA remains unknown.

We hypothesized that among patients with HVA and VIT, the rate of MCD and elevated tryptase levels would be lower than European data. We further sought to evaluate the role of tryptase as a predictive marker in patients with VIT given updated guidelines.

## METHODS

### Database

The IBM Watson MarketScan Research Database was queried for patients with a diagnosis of HVA (*International Classification of Diseases, Tenth Revision* codes T63.44, T63.45, T63.46, Z91.030, and Z91.038) and mastocytosis (*International Classification of Diseases, Tenth Revision* codes D47.01, D47.02, D47.09, C96.21, and C94.3). This database consists of deidentified

From [a]the Division of Allergy and Clinical Immunology, Department of Internal Medicine, and [b]Mary H. Weiser Food Allergy Center, University of Michigan, Ann Arbor; [c]the Division of Rheumatology, Allergy and Immunology, Department of Internal Medicine, University of North Carolina, Chapel Hill; [d]New York City College of Technology and [e]Columbia Data Analytics, LLC, New York; [f]MEF University, Istanbul, Turkey; and [g]Mayo Clinic, Rochester.

*These authors contributed equally to this work.

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Corresponding author: Charles F. Schuler IV, MD, Domino's Farms, 24 Frank Lloyd Wright Dr, Ste H-2100, Ann Arbor, MI 48106. E-mail: schulerc@med.umich.edu.



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*Abbreviations used*
ACE: Angiotensin-converting enzyme
HVA: Hymenoptera venom allergy
LOC: Loss of consciousness
MCD: Mast cell disease
SM: Systemic mastocytosis
VIT: Venom immunotherapy

outpatient, inpatient, and pharmaceutical claims of approximately 27 million privately insured patients in 2018. Complete claims originate from more than 150 large employer-sponsored health insurance plans with patient coverage in all 50 states. Real-world data from January 1, 2018, through December 31, 2018, were obtained for analysis. Eligible patients had 6 to 12 months of claims data in 2018.

## Allergy clinic patient population

We conducted a retrospective study of 161 patients with a history of systemic venom reactions and received VIT injections between 2015 and 2018 at the University of Michigan Allergy and Immunology clinic. The University of Michigan Medical School Institutional Review Board on Human Subjects reviewed and cleared the protocol. Written informed consent was not required because of the retrospective nature of the study.

## VIT protocol

Patients were selected by the treating physician to undergo VIT on the basis of available practice parameter guidelines. A history of a venomous sting followed by an allergic reaction, including a combination of diffuse urticaria, angioedema, gastrointestinal distress (including nausea, vomiting, or diarrhea), respiratory symptoms (including cough, wheeze, or dyspnea), loss of consciousness (LOC), or documented low blood pressure, was needed to begin VIT.[3,5] Patients diagnosed before the 2017 US guidelines may have started VIT on the basis of a systemic cutaneous reaction according to earlier guidelines and were not excluded from this study.[14] Positive skin or blood specific IgE testing result to honeybee, yellow jacket, yellow hornet, white-faced hornet, or wasp was required. Positive skin testing result was defined as a wheal diameter that was at least 3 mm more than that of the negative control on skin prick or intradermal testing. We note the guideline statements of uncertainty on the intradermal test cutoff; 3 mm over the negative control was used in this study because it is the consensus among the U-M allergy group where the study took place.[3] Positive blood testing result was defined as any serum IgE level to a venom above the normal range (<0.35 kU/L).[3] Patients were counseled on risks and benefits by the treating physician in the course of standard clinical care.

VIT at the University of Michigan follows US guidelines.[3] A monthly maintenance dose of 1 mL of 100 μg/mL concentrate for each venom, or 1 mL of 300 μg/mL for mixed vespid (yellow jacket, yellow hornet, and white-faced hornet), is used; 0.05 mL of dilutions down to 1:1000 of concentrate, or lower, are used to build up weekly to maintenance.

Mastocytosis was diagnosed by the treating physician, and the diagnosis was verified by the study team after reviewing the bone marrow biopsy report and tryptase values. Mastocytosis was defined according to the 2016 World Health Organization diagnosis and classification system.[15]

## Data collection

A standardized approach was used to collect prespecified variables from patients' charts. Demographic data included age, sex, and race/ethnicity. Medical history included a history of asthma, atopic sensitization, food allergy, atopic dermatitis, family history of systemic venom allergy reactions, coronary artery disease, angiotensin-converting enzyme (ACE)-inhibitor use, and beta-blocker use. A positive skin test result (a wheal diameter that was at least 3 mm more than that of the negative control) to at least 1 allergen was used to define atopy.[16] Allergens tested included trees, grasses, weeds, molds, dust mite, cat, and dog. The original venom reaction was coded according to the presence or absence of hives/rash, angioedema, respiratory symptoms (cough, dyspnea, or wheezing), gastrointestinal symptoms (nausea, vomiting, diarrhea), flushing, LOC, and low blood pressure. All reactions were graded I to IV on the basis of a modified Mueller anaphylaxis scale.[17]

Venom skin testing was recorded. For both skin prick and intradermal testing, wheal and flare in millimeters were recorded. For blood testing, total IgE and individual venom IgE levels were recorded. Sensitivity to a venom was recorded as a positive skin or blood test result.

VIT characteristics were recorded, including the time to maintenance, time on maintenance, total reactions, large local reactions, and systemic reactions (diagnosed by the treating physician).

Subsequent venom reactions in the field after starting VIT were recorded identically as the original venom reaction. Tryptase laboratory order status, draw status, date, and the value were recorded. If a bone marrow biopsy occurred, the pathologic presence of MCD, subtype, and number of major and minor criteria for mastocytosis were recorded.[18,19]

## Statistical analysis

IBM SPSS version 22 (Armonk, NY) statistical software and GraphPad Prism (San Diego, Calif) were used to perform all statistical analyses. Potentially significant ($P < .2$) associations between patient characteristics and data of interest were initially evaluated via bivariate correlation and chi-square analysis. Linear or logistic regression analysis was then performed as appropriate on all potentially significant variables to create multivariate associations. A Cochran-Mantel-Haenszel test was used to compare the prevalence of mastocytosis in patients with HVA compared with those with mastocytosis without HVA in the database; this was stratified by adult versus pediatric patients.

# RESULTS

## Database results

The database query included 27,299,530 distinct patients in the calendar year 2018. This revealed a prevalence of 166.8 per 100,000 for HVA overall. Mastocytosis prevalence was 10.1 per 100,000 overall and 96.7 per 100,000 (or 0.0967%) among patients with HVA in 2018; an odds ratio of 9.7 (95% CI, 7.2-13.1; $P < .0001$) was noted when comparing mastocytosis in patients with HVA compared with those without in 2018 (Fig 1). Among adult (age 18 years and older) patients, the odds ratio was 14.3 (95% CI, 10.5-19.6; $P < .0001$). Among pediatric (age <18 years) patients, there was no statistical significance (odds ratio, 2.4; 95% CI, 0.9-6.4; $P = .07$).

## Patient characteristics

Given the increased prevalence of mastocytosis in real-world data, we investigated the data from our allergy practice in patients with systemic reactions to Hymenoptera undergoing VIT. University of Michigan is a referral center for MCD. Table I presents the demographic and disease-specific characteristics for the patients in the University of Michigan cohort. The mean age was 47.6 years and ranged from 7 to 81 years; 41% were female, 24% carried a diagnosis of asthma, 41% had a history of atopic sensitization to a nonvenom allergen, and 8% had a family history of venom allergy.

The average Mueller anaphylaxis grade for the patients' original reactions was 2.90. This included 34% of patients with a documented low blood pressure and 26% of patients who lost consciousness. Furthermore, 66% experienced hives or rash, 61% angioedema, 48% respiratory symptoms, and 12%

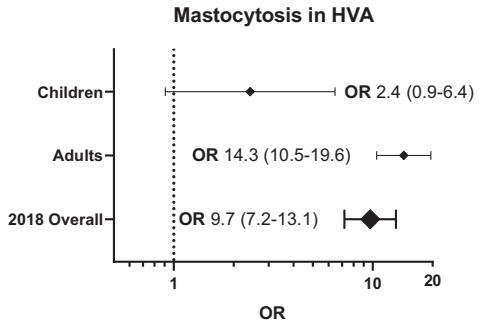


**FIG 1.** In 2018, the prevalence of mastocytosis among patients with Hymenoptera allergy was 9.7 times more than the prevalence among the US general population. *OR,* Odds ratio.

gastrointestinal symptoms. A total of 71% of patients were sensitized to honeybee, 85% to yellow jacket, 68% to yellow hornet, 73% to white-faced hornet, and 68% to wasp. During VIT, 10% experienced a systemic reaction.

### Impact of VIT on venom allergy course

VIT was effective in this venom allergy population. Among these 161 patients who began immunotherapy, 26 (16%) suffered a subsequent venom reaction (Table I). The mean Mueller grade of these subsequent reactions was 0.96 (Table I), significantly lower than the mean grade of initial reactions (Fig 2, *A*). This shows that venom reactions after VIT were less frequent and less severe than before VIT started.

We sought to find variables associated with a subsequent venom reaction after VIT initiation. Using logistic regression, the only significantly correlated variable was a family history of a systemic venom reaction, with an odds ratio of 8.8 ($P = .049$) (Table II). Four percent of patients who did not have subsequent venom reactions had a family history of a systemic venom reaction, significantly fewer than the 25% rate in patients who did have a subsequent venom reaction (Fig 2, *B*).

### Impact of guideline update on practice

American practice guidelines published in January 2017 recommend measuring tryptase levels for patients with cardiovascular compromise with venom reactions; these guidelines suggest consideration of tryptase measurement for all patients with evidence of venom anaphylaxis.[3] We sought to evaluate the impact of these guidelines on clinical practice in an academic allergy center. Among patients who did not lose consciousness during the initial venom reaction, the rate of tryptase measurement was 52%, significantly lower than the 81% among patients who lost consciousness during the initial reaction (Fig 3, *A*). Before 2017, the rate of tryptase measurement in patients with VIT was 59%; after 2017, the rate was 100%, significantly higher (Fig 3, *B*).

### Elevated tryptase and clonal MCD in the VIT population

We found 9 patients (5.6%) to have a baseline tryptase level greater than 11.5 ng/mL. Among these, 4 patients underwent bone marrow biopsy and 3 (1.8% of total) had clonal MCD. Two of these had indolent SM and 1 had monoclonal mast cell activation syndrome. These patients had significantly higher tryptase levels than patients who had a tryptase measured but no known MCD (Fig 4, *A*).

We sought to evaluate whether tryptase levels correlate with other key features of HVA. Among patients who had a tryptase level, tryptase did not correlate with the initial reaction Mueller anaphylaxis grade (Fig 4, *B*). Elevated tryptase levels appeared in patients throughout the grading scale. We also sought whether tryptase or other variables might correlate with a low blood pressure, an indicator of cardiovascular compromise, during the initial reaction. On logistic regression the only significantly correlated variables were LOC, with an odds ratio of 12.9 ($P < .0001$), and having a tryptase drawn, with an odds ratio of 2.6 ($P = .039$) (Table II). Tryptase level, whether analyzed as a continuous variable or when broken into discrete groups of 0 to 5 ng/mL, 5 to 11.4 ng/mL, and higher than 11.4 ng/mL, did not correlate with low blood pressure during the initial reaction. However, tryptase levels divided according to the same levels did correlate with LOC. Patients with tryptase levels between 5 and 11.4 ng/mL had the highest rate of LOC at 50%, significantly higher than the rate of 11% in those with a tryptase level greater than 11.4 ng/mL (Fig 4, *C*).

Because systemic reactions during VIT are a key adverse effect and worse reactions have been correlated with higher tryptase levels previously,[9] we evaluated whether this was true in our population. We found a significantly higher mean tryptase level among patients who had a systemic VIT reaction versus patients who did not (Fig 4, *D*). Furthermore, to find variables correlated with having a systemic VIT reaction, we used a multivariate logistic regression that involved all bivariate associations where *P* was less than .2; the only significantly correlated variable was tryptase level, with an odds ratio of 1.3 ($P = .027$) per unit increase in tryptase level (Table II). Notably, beta-blocker and ACE-inhibitor use did not correlate with the presence, number, or severity of a systemic VIT reaction.

## DISCUSSION

VIT is an effective preventative therapy for HVA.[3,5] US guidelines recommend considering a baseline tryptase level for all patients with HVA undergoing VIT and outright recommend to check in severe venom anaphylaxis.[3] Given a high rate of MCD among patients with HVA, up to 7% to 11%, some authors suggest measuring tryptase values in all patients with VIT.[6,7,20] SM is associated with failure of VIT, prompting the noted increased vigilance.[10] Bonadonna et al[7] found that among patients with HVA, 11.6% had tryptase levels higher than 11.4 and clonal MCD was detected in 90.9% of patients with elevated tryptase who underwent further evaluation; at a minimum, 5.5% of the total (a rate of 5,500 per 100,000) were diagnosed with SM. Furthermore, one study suggests that patients with severe hypotension and normal basal tryptase values have rates of MCD up to 75%.[21] However, a recent publication from Israel demonstrated an MCD rate of 3.8% (or 3,800 per 100,000) among patients with HVA,[13] lower than the figures cited in European data. The rate, to our knowledge, has not been reported in a US population. In this work, we report an MCD rate among patients with HVA of 0.097% in the US population. Although this rate cannot be statistically compared directly to the European or Israeli reports[7,13] because the current estimate encompasses a data set of millions versus previous reports involving hundreds of patients, this reported rate is qualitatively lower than previous reports by more

**TABLE I.** The baseline characteristics of the patient population are listed in aggregate and by adults (age 18 y and up) and children (age < 18 y)

| Patient characteristic | All patients (n = 161) | Adults (n = 147) | Children (n = 14) |
|---|---|---|---|
| Demographic | | | |
| Age (y), mean (range) | 47.6 (7-81) | 50.8 (18-81) | 13.2 (7-17) |
| Sex: female, n (%) | 66 (41) | 65 (44) | 1 (7) |
| General disease history, n (%) | | | |
| History of asthma | 39 (24) | 35 (24) | 4 (29) |
| History of other atopic sensitization | 66 (41) | 63 (43) | 3 (21) |
| History of atopic dermatitis | 15 (9) | 10 (7) | 5 (36) |
| History of food allergy | 8 (5) | 7 (5) | 1 (7) |
| Family history of venom allergy | 13 (8) | 9 (6) | 4 (29) |
| Beta-blocker use | 7 (4) | 7 (5) | 0 (0) |
| ACE-inhibitor use | 9 (6) | 9 (6) | 0 (0) |
| Original venom reaction | | | |
| Hives or rash, n (%) | 106 (66) | 96 (65) | 10 (71) |
| Angioedema, n (%) | 99 (61) | 88 (60) | 11 (79) |
| Respiratory symptoms, n (%) | 78 (48) | 71(48) | 8 (57) |
| Gastrointestinal symptoms, n (%) | 19 (12) | 15 (10) | 4 (29) |
| Low blood pressure documented, n (%) | 54 (34) | 53 (36) | 1 (7) |
| LOC, n (%) | 42 (26) | 41 (28) | 1 (7) |
| Mueller anaphylaxis grade, mean ± SD | 2.90 ± 0.88 | 2.92 ± 0.90 | 2.71 ± 0.61 |
| Venom sensitization, n (%) | | | |
| Honeybee | 115 (71) | 107 (73) | 8 (57) |
| Yellow jacket | 137 (85) | 127 (86) | 10 (71) |
| Yellow hornet | 110 (68) | 101 (69) | 9 (64) |
| White-faced hornet | 117 (73) | 107 (73) | 10 (71) |
| Wasp | 110 (68) | 101 (69) | 9 (64) |
| Venom IT course | | | |
| Systemic reaction to IT, n (%) | 16 (10) | 15 (10) | 1 (7) |
| Subsequent venom reaction, n (%) | 24 (15) | 18 (12) | 6 (43) |
| Subsequent venom reaction Mueller grade, mean ± SD | 0.96 ± 0.98 | 1.13 ± 0.97 | 0.57 ± 0.98 |
| Tryptase measurement | | | |
| Tryptase drawn, n (%) | 99 (61) | 91 (62) | 8 (57) |
| Tryptase value (ng/mL), mean (range) | 5.4 (1.5-20.9) | 5.5 (1.5-20.9) | 4.4 (2.3-8.4) |
| MCD, % all patients (% if tryptase measured) | 1.9 (2.6) | 2.0 (3.2) | 0 (0) |

Mueller grading delineated in the Methods section.[17]

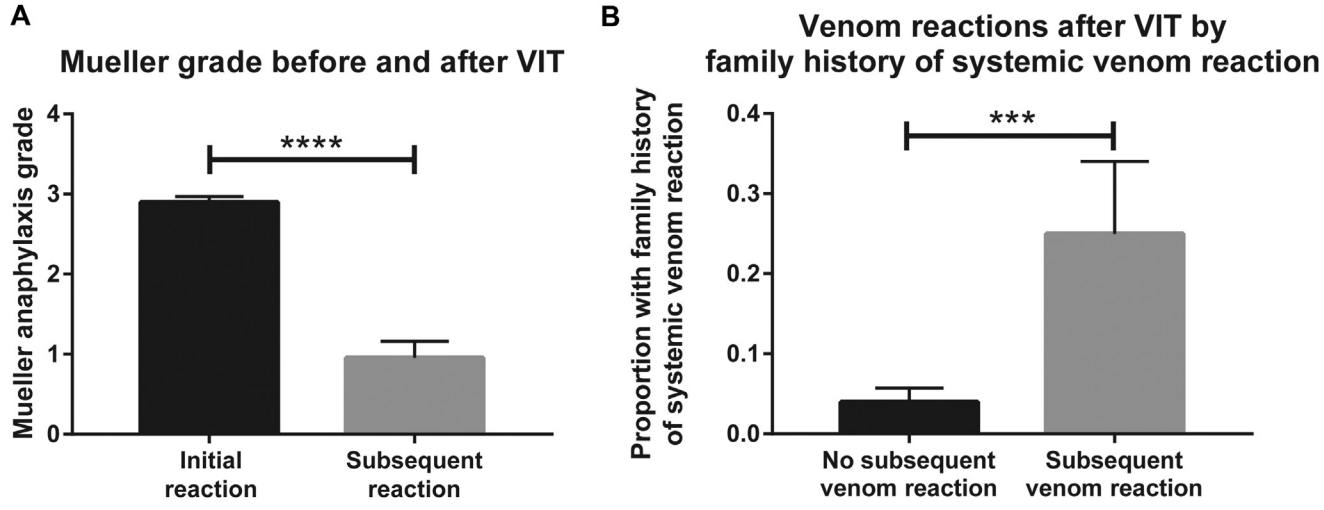


**FIG 2. A,** Mueller grade of initial reaction (mean, 2.90; n = 158) compared with Mueller grade of any subsequent reactions (mean, 0.96; n = 23). **B,** The proportion of patients with a family history of a systemic venom reaction is stratified according to whether the patient did not (4%; n = 126) or did (25%; n = 25) have a subsequent venom reaction after a VIT course. Data represent mean ± SEM. ***$P$ < .001, ****$P$ < .0001.

**TABLE II.** Results of multivariate logistic regressions

| Dependent variable | Independent variables | Odds ratio | *P* value |
|---|---|---|---|
| Systemic immunotherapy reaction | Tryptase | 1.3 | .027 |
| Low blood pressure on first reaction | LOC on first reaction | 12.9 | <.001 |
| | Tryptase drawn | 2.6 | .039 |
| Subsequent venom reaction | Family history of systemic venom reaction | 8.8 | .049 |

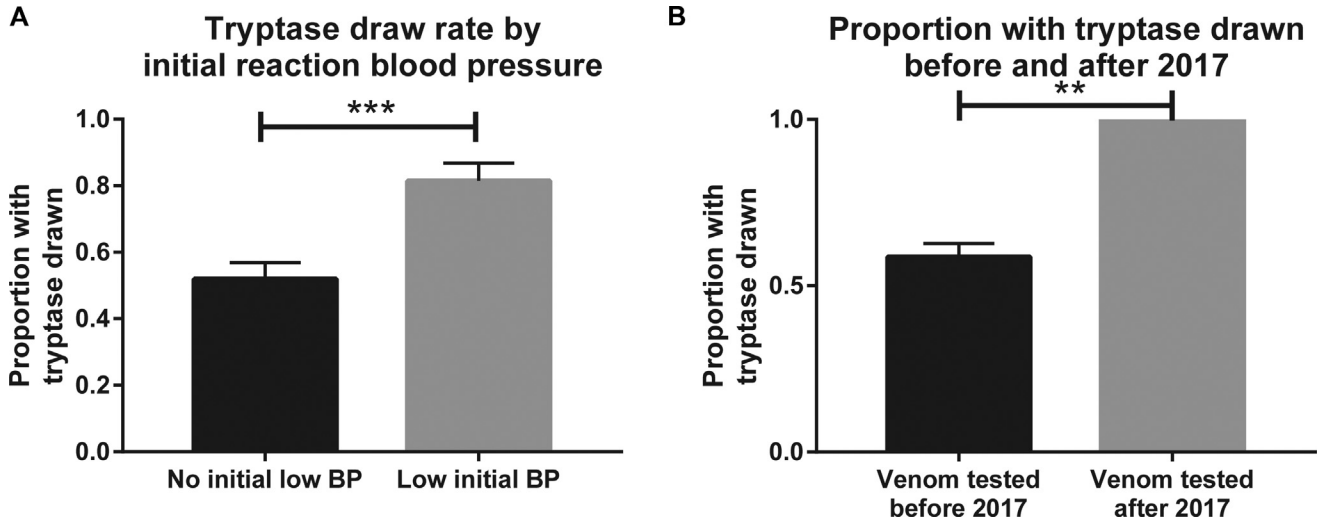


**FIG 3. A,** Rate of tryptase measurement stratified by BP drop presence (52%; n = 104) or absence (81%; n = 54) at initial reaction. **B,** Rate of tryptase measurement rate stratified by date, before 2017 (59%; n = 150) or after the start of 2017 (100%; n = 11). *BP,* Blood pressure. Data represent mean ± SEM. $^{**}P < .01$, $^{***}P < .001$.

than an order of magnitude. One explanation for the higher previously reported rate could be that previous studies occurred mainly within referral centers for mastocytosis and may have carried a selection bias.

Previous work suggests that 56% to 94% of adults report at least 1 lifetime Hymenoptera sting,[22] and the rate of systemic reactions among those who are stung is 0.5% to 3.3% in the United States[23] and 0.3% to 7.5% in Europe.[5] We report a 1-year prevalence of 0.167% in 2018 in a US cohort, lower than previous reports. Another explanation could be that our data include subjects with 6 to 12 months of data, which might lower the rate of HVA detected here, because some patients may not have had claims data during this period. This is a limitation shared with other claims database–based analyses. Furthermore, the database used in this study does not necessarily include patients not insured privately, so the population may not fully represent the entire US population, thereby affecting prevalence. The rate of systemic reactions to insects in the United States and Europe is similar, suggesting similar rates of Hymenoptera allergy; this could change with variances in insect species' distribution. For example, climate change may promote habitats favorable to invasive insects[24]; as the number of insect stings changes by region, the incidence of HVA may also change because recurrent stings have been described as a risk factor for HVA.[23] Another factor that may affect the rate of MCD within the HVA population is the total MCD burden by population; the prevalence of mastocytosis in the general population is estimated to be 3 to 13 per 100,000 inhabitants.[25] Our finding of 7.7 per 100,000 falls within the previously reported range. Thus, there might be a disproportionate change in the incidence of HVA relative to the incidence of mast-related diseases.

Another consideration is the etiology of an elevated tryptase. It has been estimated that 4% to 6% of the population has an elevated tryptase.[12] Most of these patients do not have a clonal MCD. Hereditary alpha-tryptasemia (HAT) is a recently described autosomal-dominant trait caused by increased monoallelic α-tryptase copy number at *TPSAB1*.[12] Much of the previous work examining elevated serum tryptase in patients with HVA was performed before the recognition of HAT as a distinct entity, which may have impacted MCD estimates at that time. It has only been recently that the role of HAT in HVA has been examined. Cohort studies have suggested that HAT is associated with more severe HVA, but may not affect the rate of HVA because the rate of HAT in some patient cohorts with HVA is similar to that of the general population.[26,27] HAT may be overrepresented in patients with clonal MCD, and these may have a synergistic effect on severity of anaphylaxis.[26,27] If HAT does affect anaphylaxis severity, this may explain why some patients with MCDs have more severe HVA versus others and why elevated serum tryptase without clonal MCD has been at times associated with HVA severity. The role of HAT in HVA is an area that requires further investigation.

Race is increasingly recognized as a factor in many atopic diseases.[28] It has been implicated in not only outcomes disparities but also the immunology and genetics of atopy. The United States has a racially and ethnically diverse population. This heterogeneity of this group could explain differences in MCD and HVA in the US population compared with Europe. Role of ethnic background

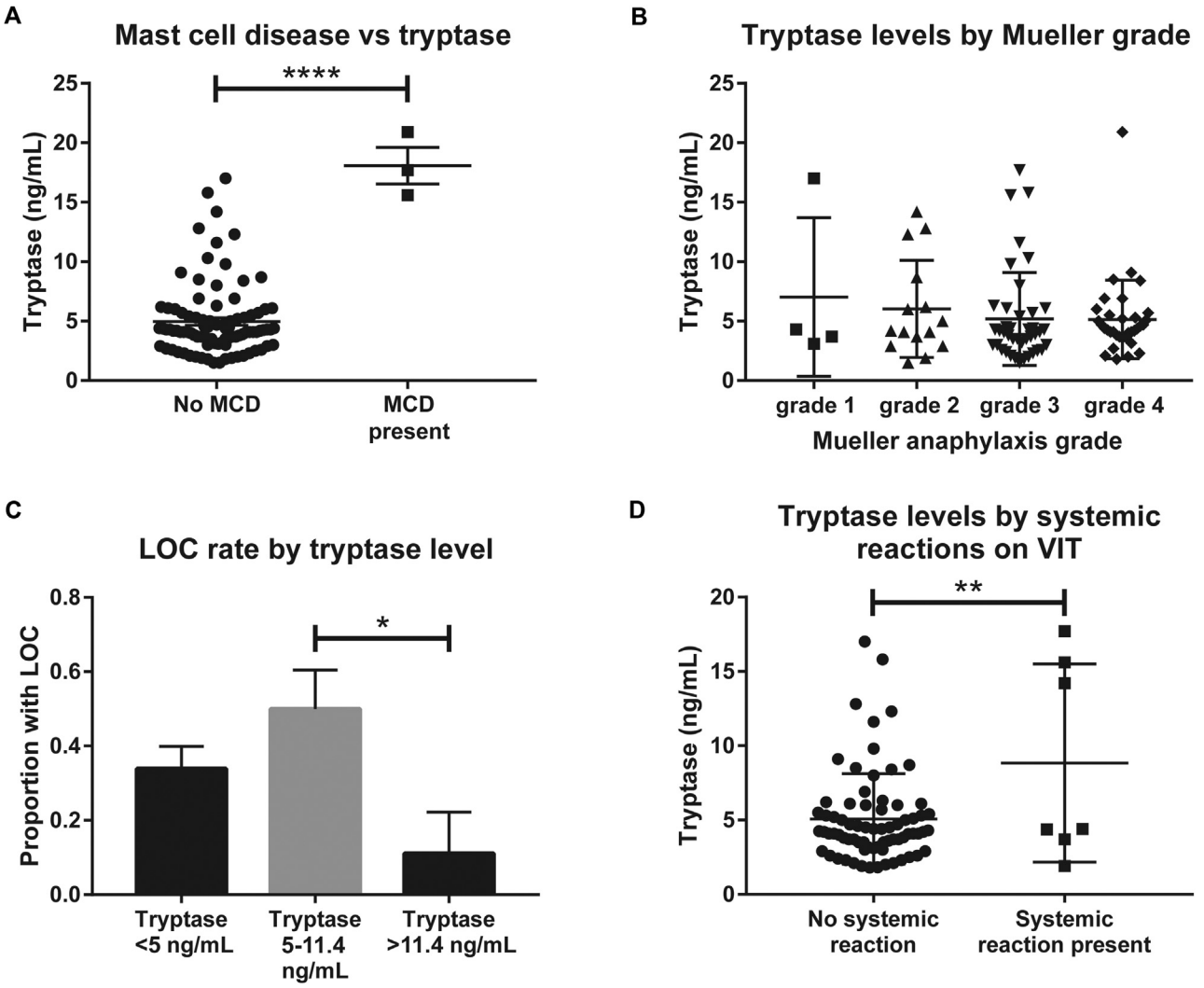


**FIG 4.** **A,** Tryptase level stratified by whether an MCD was present (mean, 18.0; n = 3) or not present (mean, 5.0; n = 93). **B,** Tryptase levels are plotted according to the Mueller grade of the patient's initial venom reaction. Mean tryptase: grade 1 = 7.0 (n = 4), grade 2 = 6.0 (n = 15), grade 3 = 5.2 (n = 41), grade 4 = 5.1 (n = 34). **C,** The proportion of patients with LOC is plotted on the basis of tryptase level, with ranges of less than 5 ng/mL (34%, n = 62), 5 to 11.4 ng/mL (50%, n = 24), and more than 11.4 ng/mL (11%, n = 9). **D,** Tryptase levels are plotted for patients who did (mean, 8.8; n = 7) or did not (mean, 5.1; n = 73) have systemic reactions during VIT. Data represent mean ± SEM. **P* < .05, ***P* < .01, *****P* < .0001.

in mast cell–related disease and HVA are 2 areas that require further investigation.

The lower rate of MCD in this study may be due to various factors. The IBM database relies on the proper coding of the diagnoses of Hymenoptera allergy and mastocytosis. The accuracy of coding can vary, with literature suggesting rates of error from 0% to 70%.[29] This suggests that a significant number of patients with HVA are not screened for MCD. Another limitation is the method diagnosis for HVA, because the initial reaction and allergy testing are not reported. Because up to 25% of adults may have Hymenoptera sensitization,[30] it is possible that patients with nonanaphylactic insect sting reactions and sensitization to Hymenoptera were mislabeled as HVA.

The role of baseline tryptase in the course of VIT has been explored. Higher basal tryptase levels have been proposed to predict a high risk of VIT side effects, particularly during buildup.[9] Elevated basal tryptase has also been associated with severe sting reactions,[8,31,32] including hypotension and fatality.[33] In this work, the tryptase level was not correlated with the severity of the initial reaction, though this study involves only those on VIT, which may be a confounding factor. In fact, patients with tryptase levels higher than 11.4 ng/mL had less frequent LOC than those with lower tryptase levels (Fig 4, *C*). We do note that in patients with known mastocytosis, patients with higher basal serum tryptase (eg, 40 ng/mL or above) are less likely to have anaphylaxis than those with mild to moderate elevations,[34] so perhaps a similar effect is occurring here in this broader population; more work would be needed to address this further.[11] Because our cohort specifically examined patients with VIT, we cannot assess whether tryptase levels correlate with severity of initial reactions

among patients with anaphylactic reactions versus patients with nonanaphylactic reactions (because that group does not typically undergo VIT). An elevated baseline tryptase was associated here with systemic reactions to VIT, consistent with previous published work.

Allergists may have increased suspicion of underlying mastocytosis when particular characteristics of the sting reaction are present, such as hypotension without hives, especially in males.[35] This was reflected in our data, because the treating allergist was more likely to draw a tryptase level in patients who presented with a low blood pressure (Fig 3, *A*). Furthermore, the guideline changes in the United States in 2017[3] appeared to impact practice patterns, because all patients with VIT started after 2017 had a tryptase level drawn, compared with before 2017 (Fig 3, *B*).

Previous authors have suggested no association between anaphylaxis severity and comorbidities or cardiovascular medications.[20,36] Our data were supportive of this as well; beta-blocker use, ACE-inhibitor use, and cardiovascular disease were not associated with initial reaction severity, subsequent reaction rate or severity, nor with the rate of systemic reactions while patients were on VIT.

Previous literature has suggested an association between HVA and MCD based on several observations. The prevalence of HVA in SM is higher than in the general population, and HVA represents the most common anaphylaxis trigger in adult patients with mastocytosis; there is also more frequent clonal MCD in patients with systemic HVA than in the general population.[37] This study supports a relationship between HVA and mastocytosis, with the prevalence of mastocytosis among patients with HVA being almost 10-fold higher than among the general population.

## Conclusions

Mastocytosis may be less common in the US population compared with European reports with systemic venom reactions, but a strong association remains between HVA and mastocytosis. In this population of patients with VIT, serum tryptase values do not correlate with severity of venom reactions; indeed, higher levels may correlate with less frequent LOC. Baseline serum tryptase elevation does correlate with more frequent systemic VIT reactions. Beta-blocker and ACE-inhibitor use in this population do not correlate with the frequency or severity of venom or VIT reactions. Overall, these data suggest that although baseline serum tryptase may help identify patients with MCD among the HVA population and help predict systemic reactions to VIT, the MCD rate may be lower in this US population than in other populations.

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**Clinical implications: Mastocytosis is less common among patients with HVA in the United States than in Europe. Basal serum tryptase elevations may predict VIT reactions.**

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