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In cold blood: Observational descriptive review of Eastern Massasauga rattlesnake bites reported to a single poison center over time

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ABSTRACT

The Eastern Massasauga rattlesnake (*Sistrurus catenatus catenatus*) is a pit viper indigenous to the Great Lakes region and the only venomous snake native to Michigan. It is small-to-medium, thick-bodied with dark brown, bow-tie shaped blotches. Its behavior is described as reclusive and docile and it prefers damp habitats. The venom of the Eastern Massasauga is primarily cytotoxic and hemotoxic. Previous literature describes severe coagulopathies following Eastern Massasauga envenomings, with some resulting in death. The objective of this study was to characterize Eastern Massasauga envenomings in humans reported to the Michigan Poison & Drug Information Center from 2003 to 2020, including a description of clinical manifestations, incidence and characterization of coagulopathies, and medical outcome severities. This was a retrospective review of Eastern Massasauga snakebites reported to our state poison center over time. Coagulopathies were classified according to previous toxicological snakebite literature. The degree of envenoming was scored using an institutional guideline, representing a modified version of validated snakebite severity score system. Our longitudinal review demonstrated Eastern Massasauga bites led to clinically significant toxicity, including persistent, recurrent, and late coagulopathies, though with low incidence of bleeding events. Cases typically resolved with use of antivenom. This, to our knowledge, is the largest descriptive case series characterizing Eastern Massasauga snakebites.

1. Introduction

Rattlesnakes account for the majority of morbidity and mortality secondary to venomous snakebites in the United States (US) (Levine et al., 2014). The only venomous snake native to Michigan is the Eastern Massasauga rattlesnake (*Sistrurus catenatus catenatus*) according to the Michigan Department of Natural Resources. The Eastern Massasauga belongs to the Crotalinae subfamily (pit vipers) of the Viperidae family and is indigenous to the Great Lakes region (Sing et al., 1994; Hankin et al., 1987). It is a small-to-medium, thick-bodied rattlesnake that is gray, light brown, or tan with dorsal dark brown, bow-tie-shaped blotches (Fig. 1) (United States Fish and Wildlife Service, 2019). It shares similar morphological characteristics to other pit vipers including a triangular head, elliptical pupils, and heat-sensing pits between the eyes and nostrils. One unique feature is the Massasauga's nine symmetrical plates arranged in rows on the crown (aka crown shields) that makes it distinguishable from true rattlesnakes (*Crotalus* spp.) (Hankin et al., 1987; Minton, 1983). This subspecies prefers damp habitats and is mostly found in prairie marshes, bogs, and grasslands (Minton, 1983). Despite general physical similarities to crotalids, Eastern Massasaugas are more reclusive and docile (Sing et al., 1994). As such, a relative dearth of literature exists surrounding toxicity in humans following envenoming.

Venom from the Eastern Massasauga, similar to other rattlesnakes, is a complex mixture of enzymatic and non-enzymatic proteins. Many of the protein-based toxins are hemotoxic and can lead to consumptive coagulopathies (Isbister, 2009; Lisle and Chiucchi, 2011). Coagulopathies secondary to pit viper envenomings have typically been described as short-lived with late or delayed coagulopathies being infrequently reported; these coagulative abnormalities are typically not associated with bleeding events (Levine et al., 2014; Boyer et al., 1999). Case reports have described severe coagulopathies following Eastern Massasauga envenomings, with some resulting in death in untreated individuals (Sing et al., 1994).

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1.1. Objectives

We present a descriptive case series of Eastern Massasauga rattlesnakebites reported to the Michigan Poison & Drug Information Center over an 18-year period. Our objective was to document and characterize Eastern Massasauga envenomings in humans, including the description of clinical manifestations, incidence and characterization of coagulopathies, treatment course, and medical outcome severities.

2. Materials & methods

This was a retrospective observational case series involving all Eastern Massasauga rattlesnakebites reported to a single poison center from January 1, 2003 to December 31, 2020. Michigan has approximately 10 million residents with one poison center. Calls to our state poison center are voluntary, experiencing an annual call volume greater than 60,000. Poison center data is collected by trained staff composed of Specialists in Poison Information (SPI) and Poison Information Providers (PIP), who are nurses, pharmacists, or physicians. For each case, SPIs and PIPs create a chart within our secure electronic poison center database. Relevant exposure, demographic, and clinical data are recorded along with standardized codes for signs, symptoms, and treatment interventions based on criteria delineated by the American Association of Poison Control Centers' (AAPCC) National Poison Data System (NPDS) Coding Manual (American Association of Poison Control Centers, 2019).

2.1. Experimental design

We queried our poison center database from January 1, 2003 to December 31, 2020 for human snakebites. Cases of wild unknown species of snakebites that resulted in envenoming-type effects similar to the Eastern Massasauga were included as there is only one native venomous snake to humans in Michigan, as well as bites reported as Eastern Massasauga bites. The database query was performed between November 1, 2020 and January 5, 2021. Inclusion criteria involved all reported human envenomings from the Eastern Massasauga rattlesnake; all ages and both sexes were included. Exclusion criteria were reported envenomings from other snake species, non-human envenomings, and information request calls.

A total of 121 cases were initially screened from the poison center database based on preliminary pre-defined search criteria. Cases documented as 'rattlesnake envenomings' or 'unknown crotalid envenomings' were queried. From the initial screening, 37 cases were omitted as they met pre-specified exclusion criteria. Of the remaining 84 cases, a panel of two toxicologists (AK, VV) and a medical toxicology fellow (EJ) reviewed individual cases to determine whether inclusion criteria were satisfied. Nine additional cases were removed following re-review for questionable evidence of a snakebite including lack of any discernible puncture wound and/or no visual or physical confirmation of a snake. Cases of potential 'dry bites', consisting of the evidence of puncture wounds but with no clinical symptomatology, were included. Therefore, based on the panel consensus, a total of 75 cases were included in the final study analysis (Fig. 2). All cases meeting inclusion criteria were de-identified for subsequent review and analyzed for descriptive findings. This study was approved by the Institutional Review Board (IRB 20-10-2872; Approval date, March 24, 2021).

2.2. Data abstraction

Pertinent demographic and clinical data abstracted from our database were entered into an electronic data spreadsheet (Excel, 2019; version 1808, Microsoft Corp., Redmon, WA). Data abstracted included age, sex, geographical location, anatomical location of the bite, presence of puncture wounds, previous bite history, pre-hospital interventions, clinical signs and symptoms, confirmation of snake species, coagulation laboratory results, whether fasciotomy was performed, if antivenom was used, specific antivenom product used, number of antivenom vials, adverse reaction(s) following antivenom administration, and medical outcome severity. Medical outcome severities were based on 'related' or 'unknown if related' clinical effects in the AAPCC NPDS Coding Manual (American Association of Poison Control Centers, 2019) [see Appendix].

2.3. Likelihood of envenoming

The data obtained were reviewed further for the likelihood of true envenoming by the Eastern Massasauga as well as envenoming grade. The definitions and results were agreed upon by all three panelists. The likelihood of true identification of the Eastern Massasauga was graded as well. Snake identification was classified as follows: *positive* identification of Eastern Massasauga was determined if a photograph was given and identified by a herpetologist or the Michigan Department of Natural Resources personnel or the snake was brought in dead or alive, *highly suggestive* identification relied on a patient description or identification (rattle present or heard) plus symptoms consistent with envenoming by the Eastern Massasauga, and *low confirmation* was deemed if it was unconfirmed by any other means.

Fig. 1. Eastern Massasauga rattlesnake (U.S. Fish and Wildlife Service, 2019).

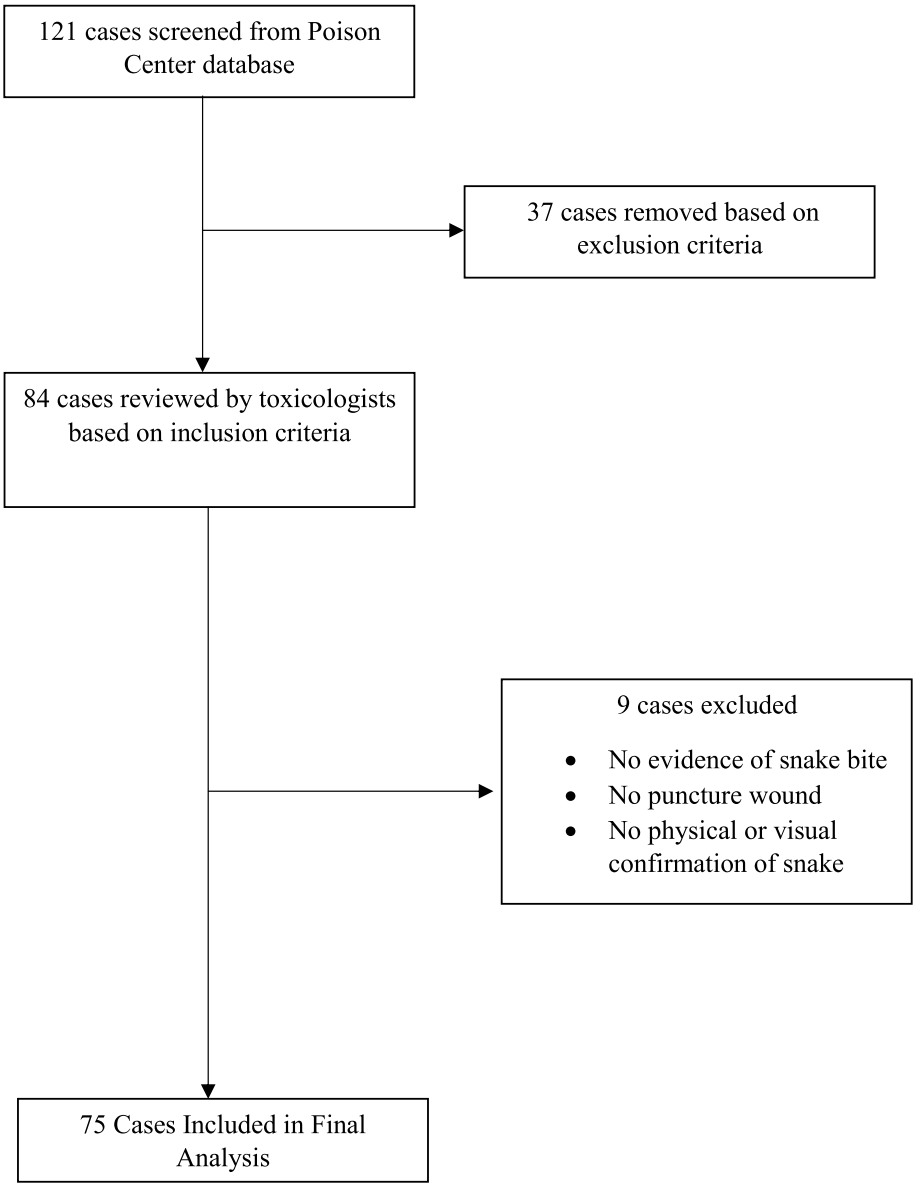

Fig. 2. Study case selection process.

2.4. Envenoming classification

The degree of envenoming was graded according to our institutional guideline, which is a modified version derived from both a validated snakebite severity score system and prominent toxicologic emergency reference text (Table 1) (Nelson et al., 2019; Dart et al., 1996). County locations of reported envenomings were documented with frequencies subsequently plotted on a state map to demonstrate geographical distribution and dispersion (Fig. 3).

Following individual case reviews by the panelists, each case was discussed during in-person meetings or remote conference calls to confirm agreement with grading and classifications. Any cases with discrepancies in categorization or classification were re-reviewed and deliberated upon until a complete consensus was reached.

2.5. Coagulopathy classification

Coagulopathy was defined as thrombocytopenia with platelets $\leq$120 K/mm^3, hypofibrinogenemia $\leq$170 mg/dL, and/or prolongation of prothrombin time (PT) $\geq$ 15 s (Ruha et al., 2017). 'Stabilized' coagulopathies corrected within 48 h and did not recur; 'recurrent' coagulopathies were recognized within the first 12 h, normalized, and subsequently recurred at a later time; 'late' coagulopathies occurred *de novo* 12 h or more following first antivenom administration; 'persistent' coagulopathies did not normalize at the time of hospital discharge (Boyer et al., 1999).

2.6. Bleeding categorization

Bleeding events were also categorized. 'Major bleeding' was defined as fatal bleeding, bleeding associated with hemodynamic instability, bleeding requiring an invasive therapeutic intervention (e.g., endoscopy), bleeding requiring transfusion of one or more units of packed red blood cells, or bleeding into an enclosed space (e.g., retroperitoneal or intracranial). 'Minor' bleeding was any bleeding resulting in admission or prolonged observation, but not requiring the administration of blood products or performance of any procedures. 'Trivial' bleeding did not require any intervention or prolonged observation and included persistent oozing from puncture wounds and self-limited bleeding (e.g., epistaxis or hemorrhoid bleeding) (Levine et al., 2014).

Table 1
Modified envenoming grading scale.

Grade	Criteria
No envenoming	● Fang marks only ● No systemic effects ● No abnormalities, no evidence of bleeding
Minimal	● Swelling, pain, tenderness, or ecchymosis limited to local bite area ● No systemic effects ● No abnormalities, no evidence of bleeding
Moderate	● Swelling, pain, tenderness, or ecchymosis limited to less than one extremity ● Head, neck, or trunk: limited to within 50 cm of site ● Non-life-threatening: nausea, vomiting, oral paresthesias, abnormal taste, fasciculations ● Mild hypotension (SBP <90 mm Hg) ● Mild tachycardia (<150 bpm) ● Tachypnea ● Abnormal coagulation labs (elevated PT/INR, decreased platelets, decreased fibrinogen, elevated D-dimer) ● No clinical evidence of abnormal bleeding or clotting
Severe	● Swelling, pain, tenderness, or ecchymosis involving entire limb or potential airway compromise ● Markedly abnormal vital signs: severe hypotension (SBP <90 mm Hg), or shock, or severe tachycardia (HR > 150 bpm or less if not tolerated by patient), or severe tachypnea or respiratory insufficiency, or altered mental status ● Marked abnormal coagulation parameters with serious bleeding or potential bleeding, or platelet count <10,000 mm^3

3. Results

A total of 75 cases met study inclusion criteria (Table 2). The majority of subjects were men (60 of 75; 80%). The mean age was 36 years. Eighteen cases involved pediatric patients (≤18 years old). Moderate medical outcome severities were most common. Two cases (2.7%) were deemed to have no effect and three cases (4%) were unable to be followed as the patients left against medical advice. Based on the study envenoming grading scale, moderate envenoming was the most commonly reported classification encountered. No deaths were reported. Forty-nine cases (65.3%) reported evidence of puncture wounds. Bites were most commonly located on the hands and fingers. Prehospital interventions were documented in only seven cases (9.3%), the most frequent being wound decontamination with soap and water; there was one case of oral suction and one case of tourniquet use. The most frequently occurring signs and symptoms were edema (56 cases; 74.7%), pain (31 cases; 41.3%), and erythema (16 cases; 21.3%). A fasciotomy was performed in one case (1.3%). The fasciotomy was performed prior to any antivenom administration.

Twenty-eight cases (37.3%) involved coagulopathies based on the pre-defined study criteria. Thirteen patients had multiple derangements in the coagulation profile. Hypofibrinogenemia was most common. Persistent coagulopathies were most frequent. Three cases could not determine the type of coagulopathy as there was only one data point. There were two cases of trivial bleeding (bleeding at bite site) in which neither patient had coagulation abnormalities. One case involved minor delayed bleeding with hemoptysis, however, the patient was on chronic aspirin, clopidogrel, and warfarin therapy at baseline. This patient had hypofibrinogenemia and prolonged PT with coagulopathy defined as late and persistent. There was one case of major bleeding involving hemoptysis where the patient was given fresh frozen plasma and cryoprecipitate. This patient also had hypofibrinogenemia and prolonged PT with recurrent coagulopathy.

Antivenom was used in 40 cases (53.3%). Crotalidae polyvalent immune fab (ovine) was approved for use in the year 2000. Crotalidae polyvalent immune fab (ovine) was predominantly administered (36 cases; 90%). One case received antivenin polyvalent. One case received a combination of crotalidae polyvalent immune fab (ovine) and antivenin polyvalent. Two cases were unclear on the antivenom used. Crotalidae immune $F(ab')_2$ (equine) was not employed in any cases in this series. An average of 13 vials of crotalidae polyvalent immune fab antivenom were used in cases where the number of antivenom vials was recorded. Adverse reactions to antivenom occurred in ten cases (25%). The most common adverse reactions were rash/itching (4 cases, 5%) and fever/chills (3 cases, 4%). One case involved what appeared to be clinically consistent with serum sickness. Twelve cases (16%) were deemed a positive ID, 48 cases (64%) were highly suggestive, 15 cases (20%) were low confirmation.

4. Discussion

The Eastern Massasauga rattlesnake, also colloquially known as the swamp rattlesnake, is the only venomous snake located in Michigan. The species can also be found in other Midwestern states including Illinois, Indiana, Iowa, Minnesota, Ohio, and Wisconsin along with eastern regions like New York, Pennsylvania, and Ontario, Canada. Biologists have confirmed that less than half of the Eastern Massasauga's historical populations are in existence, with declining species populations attributed to loss and fragmentation of their wetland habitat (Choquette et al., 2012). The majority of existing populations are found in Michigan and Ontario, Canada (U.S. Fish and Wildlife Service, 2019). According to indigenous North American traditions, Massasaugas are the 'medicine keepers of the land' (COSEWIC, 2012). This species is described as evasive, preferring to retreat or use camouflage and foliage to avoid detection by predators and humans. Flooding of their habitat by rainstorms frequently leads to the Eastern Massasauga seeking higher ground; this, combined with being found closer to heat-retaining asphalt during colder temperatures, leads to the increased probability for human interactions (Hankin et al., 1987). Eastern Massasaugas have relatively small fangs that are unlikely to penetrate through gloves, clothing, and leather products (Laureano and Crowther, 2018). Thus, envenoming are rare, and severe outcomes, including death, even less common. Nonetheless, despite its small size, bites can at times result in clinically significant morbidity.

The clinical diagnosis of an Eastern Massasauga bite relies heavily upon the combination of patient history, observable signs and symptoms, and pertinent laboratory derangements since confirmation with high confidence is rare. Previous cases report similar signs and symptoms to those commonly encountered in our study, including swelling, pain, and erythema. These local findings, if left untreated, can progress to significant tissue swelling, ecchymosis, severe pain, and systemic manifestations including hemodynamic compromise, coagulopathies, and bleeding events. The extent and severity of envenoming and clinical effects are multifactorial, predicated upon variables including the age of the snake and the amount of venom injected. The majority of previously reported Eastern Massasauga snakebite cases, similar to our study, involved the administration of antivenom. A pediatric case series from Michigan concluded that Eastern Massasauga snakebite cases appear to resolve with the administration of antivenom and good supportive care (Hankin et al., 1987).

This case series characterizes envenomings secondary to Eastern Massasauga rattlesnakebites reported to our poison center over time. This, to our knowledge, is the largest existing case series in the literature of Eastern Massasauga envenomings in humans of all ages. Consistent with a previous cases series of Eastern Massasauga envenomings in children, bites most commonly occurred on the hand followed by foot/ankle and coagulopathies with varying degrees of severity were relatively common (Hankin et al., 1987; Laureano and Crowther, 2018). Some reports describe untreated Eastern Massasauga bites resulting in death due to coagulopathies (Sing et al., 1994). Derangements in coagulation studies secondary to an Eastern Massasauga bite reflect the mechanisms of the complex mixture of enzymes in its venom, including proteinase and phospholipase that target and degrade platelets, fibrinogen, and fibrin along with microvascular damage leading to endothelial dysfunction (Hankin et al., 1987; Bailey et al., 2011).

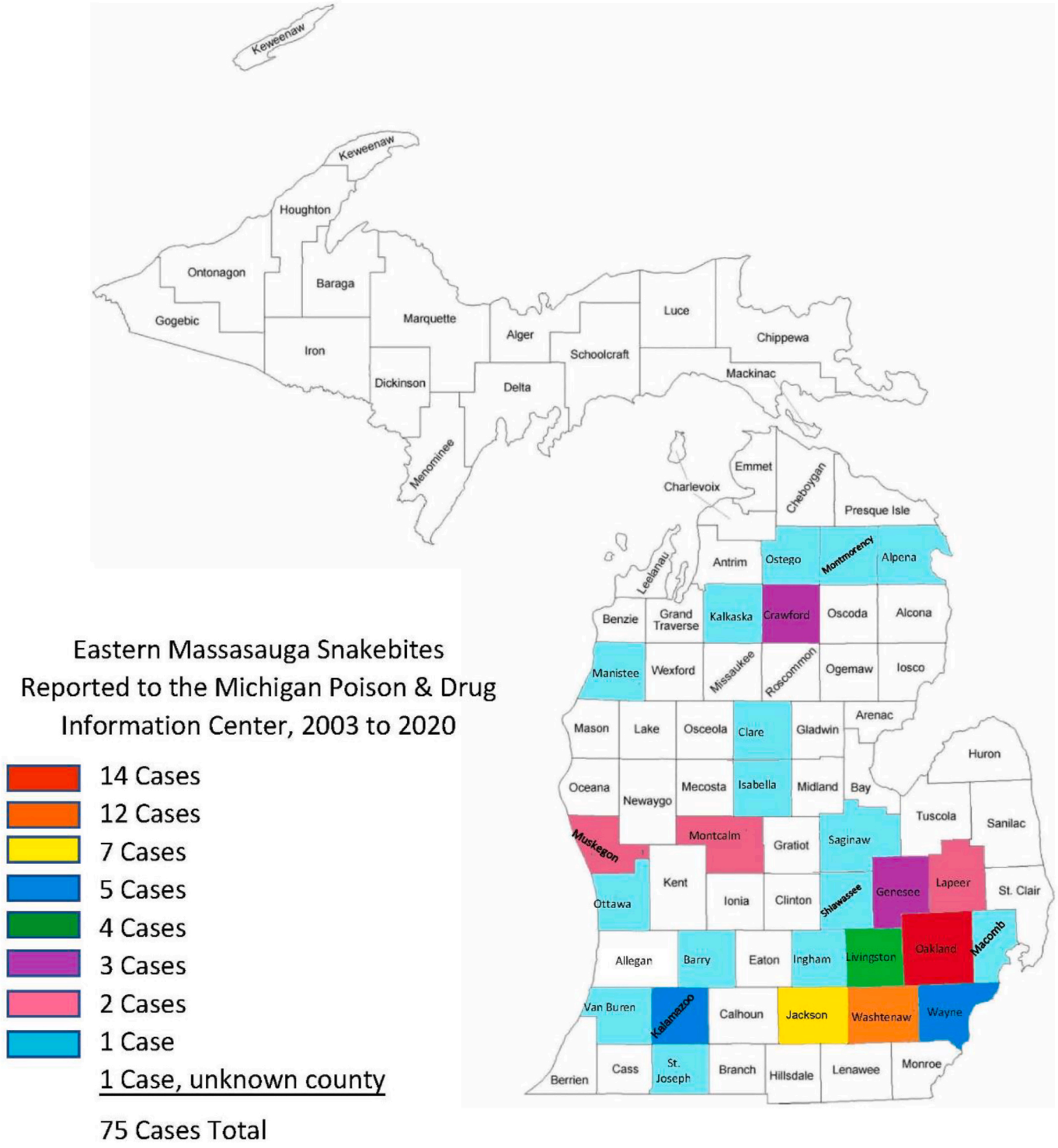

Fig. 3. Geographical distribution of Eastern Massasauga rattlesnakebites reported to state poison center.

Recurrent or persistent coagulopathy could be multifactorial. Relatively rapid clearance of Fab antivenom is associated with the return of venom antigenemia; this assumes unneutralized venom persists long after envenoming. Recurrent or persistent coagulopathies are observed more frequently after the use of Crotalidae polyvalent immune fab (ovine). Although this antivenom product is less immunogenic, it has a relatively shorter half-life than the previous antivenin (Crotalidae) polyvalent (ACP) and crotalidae immune $F(ab')_2$ (equine) (O'Brien et al., 2009). Circulating antivenom immune Fab has a half-life between 15 and 25 h, therefore the portion not bound to venom will be renally cleared (O'Brien et al., 2009). Coagulopathies could also be a consequence of a depot of unneutralized venom at the bite site; as antivenom levels fall, unneutralized venom may still be released and reabsorbed into systemic circulation leading to persistent venom effects requiring subsequent antivenom dosing. Further, the antivenom:venom complex may be too large for renal clearance, thereby providing more time for the complex to dissociate and thus leading to a recrudescence of the venom's effect. This case series suggests coagulopathy does not result in clinically significant bleeding events and the risk of late or recurrent coagulopathy is less than 10%. Furthermore, late coagulopathy is not a

Table 2
Demographic and characterization of envenoming cases and associated clinical toxicity.

Demographics	Results
Sex	
Male	60 (80%)
Female	15 (20%)
Age (years)	Mean 36 (range, 5–67 years) Median 30 18 pediatric (≤18 years)
Anatomical location of the bite	
Hand/finger	40 cases (53%)
Foot/ankle	18 (24%)
Leg	10 (13%)
Arm	7 (9%)
Signs and symptoms	
Swelling	56 cases (75%)
Pain	31 (41%)
Erythema	16 (21%)
Abrasion/scratch	8 (11%)
Bleeding at bite site	6 (8%)
Ecchymosis	6 (8%)
Numbness	5 (7%)
Vomiting	4 (5%)
Nausea	3 (4%)
Headache	2 (3%)
Tachycardia	2 (3%)
Rash	1 (1%)
Hypotension	1 (1%)
Coagulation derangement	28 in total
Hypofibrinogenemia	25 (33.3%)
Prolonged PT	14 (18.6%)
Thrombocytopenia	3 (4%)
Coagulopathy	
Persistent	11 (14.6%)
Stabilized	8 (10.6%)
Recurrent	5 (6.6%)
Late	3 (4%)
Not enough data	3 (4%)
Envenoming grade	
No envenoming	12 cases (16%)
Minimal	25 (33%)
Moderate	32 (43%)
Severe	6 (8%)
Medical outcome severity	
No effect	2 cases (3%)
Minor	19 (25%)
Moderate	34 (45%)
Major	17 (23%)
Left AMA	2 (3%)
Unable to follow	1 (1%)
Adverse effects following antivenom	
Rash/itching	4 (5%)
Fever/chills	3 (4%)
Serum sickness	1 (1%)
Difficulty breathing	1 (1%)
Warm sensation during infusion	1 (1%)
Shaking	1 (1%)
Vomiting	1 (1%)

common feature of Eastern Massasauga envenoming in contrast to up to 1/3rd of cases seen in prior case series (Ruha et al., 2011). It is unclear if this risk is further decreased with $F(ab')_2$ antivenom therapy, as has been reported elsewhere since this antivenom has not been frequently used in Massasauga envenomings (Bush et al., 2015).

The Eastern Massasauga can be confused with or misidentified as other banded snake species including the Eastern Hognose snake (*Heterodon platirhinos)*, which is also found in Michigan; however, toxicity secondary to an Eastern Hognose snakebite in humans is negligible. Other venomous snakes in relative proximity that may share a range with the Eastern Massasauga outside of Michigan include copperheads (*Agkistrodon contorix*) and timber rattlesnakes (*Crotalus horridus)* (Minnesota Department of Natural Resources, 2021). Despite the Eastern Massasauga being the only venomous snake in Michigan, there are upwards of seventeen other snake species found in the state per the Michigan Department of Natural Resources. Although these species are considered nonvenomous, bites may still potentially lead to clinical symptomatology. As such, this does not preclude the possibility of some of our reported cases being secondary to bites caused by other snakes in Michigan, highlighting the limitations implicit in poison center data and the study methodology.

Limitations of this study include the retrospective study design involving a single poison center. Inherent poison center data limitations include voluntary reporting of patient cases, reporting inaccuracies, and incomplete and inaccurate coding. Poison center data relies on passive reporting of cases from health care facilities; we lacked access to hospital medical records for all cases precluding an accurate assessment or confirmation of patient medical histories, co-morbidities, and/or prescribed or over-the-counter medications/supplements that predispose to aberrant coagulation studies or bleeding. Follow up after discharge was also voluntary and only collected in a handful of cases. We lacked any long-term follow-up and sequalae information in these patient cases. Due to the retrospective nature of the study and method of poison center case and data collection, direct confirmation of the snake species involved in every case was not feasible, often relying heavily on patient history and clinical findings. Patients deemed to have questionable snakebites were excluded, potentially underestimating the true case burden. The average time to patient presentation to a health care facility was not available, with delayed presentations invariably impacting outcome severity. The retrospective study design did not allow us to correlate venom serum levels to characterize cases with and without coagulopathies.

5. Conclusion

This is the largest case review characterizing Eastern Massasauga envenomings in humans. Our longitudinal review demonstrated Eastern Massasauga bites led to clinically significant toxicity, including persistent, recurrent, and late coagulopathies. However, incidence of bleeding was low. The majority of cases treated with antivenom resolved with positive health outcomes.

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Credit author statement

Elizabeth Jacobs: Conceptualization, Methodology, Investigation, Data Curation, Formal Analysis, Writing – Original Draft, Writing – Review & Editing, Visualization Andrew King: Conceptualization, Methodology, Investigation, Writing – Review & Editing, Supervision Varun Vohra: Conceptualization, Methodology, Investigation, Data Curation, Formal Analysis, Writing – Original Draft, Writing – Review & Editing, Visualization, Supervision, Project Administration.

Ethical statement

This retrospective study did not involve research in human subjects therefore no informed consent was obtained or necessary. No patient identifiers were abstracted or disclosed as all data was abstracted using a de-identified poison center database.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix B. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.toxicon.2021.12.004.

Appendix

American Association of Poison Control Centers National Poison Data System (version 4.1).
Medical Outcomes Designation.

Designation	Definition
No Effect	The patient developed no symptoms as a result of the exposure. Follow-up is required to make this determination unless the initial regional poison center call occurs sufficiently long enough after the exposure that there is reasonably certainty that no effects will occur.
Minor Effect	The patient exhibited some symptoms as a result of the exposure, but they were minimally bothersome to the patient. The symptoms usually resolve rapidly and often involve skin or mucous membrane manifestations. The patient has returned to a pre-exposure state of well-being and has no residual disability or disfigurement. Follow-up is required to make this determination unless the initial regional poison center call occurs sufficiently long enough after the exposure that there is reasonable certainty that the clinical effect(s) will not worsen. Symptomatic patients must be followed until symptoms have resolved or nearly resolved, unless the residual symptoms are anticipated to be long-term and of minimal clinical significance
Moderate Effect	The patient exhibited symptoms as a result of the exposure which are more pronounced, more prolonged or more of a systemic nature than minor symptoms. Usually some form of treatment is or would have been indicated. Symptoms were not life-threatening and the patient has returned to a pre-exposure state of well-being with no residual disability or disfigurement. Follow-up is required to make this determination unless the initial regional poison center call occurs sufficiently long enough after the exposure that there is reasonable certainty that the clinical effect(s) will not get worse. Symptomatic patients must be followed until symptoms have resolved or nearly resolved, unless the residual symptoms are anticipated to be long-term and of minimal clinical significance.
Major Effect	The patient has exhibited symptoms as a result of the exposure which were life-threatening or resulted in significant residual disability or disfigurement. Follow-up is required to make this determination unless the initial regional poison center call occurs sufficiently long enough after the exposure that there is reasonable certainty the clinical effect(s) will not get worse. Symptomatic patients must be followed until symptoms have resolved or nearly resolved, unless the symptoms are anticipated to be long-term or permanent.

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