What History, Examination, and Laboratory Findings Suggest Severe Snake Envenomation?

TAKE-HOME MESSAGE

Time from bite to care of greater than or equal to 6 hours, patient age 12 years or younger, large (adult) snake size, ptosis, bleeding distal to the bite site, hypofibrinogenemia, and thrombocytopenia increase the likelihood of severe snake envenomation, whereas bites from *Agkistrodon* (copperheads and cottonmouths) are less likely to result in severe envenomation. Few features can exclude severe envenomation or the need for antivenom.

METHODS

DATA SOURCES

A medical librarian identified English-language studies from PubMed and EMBASE through October 3, 2017, evaluating clinical features that predict severe Crotalinae envenomation.[1] Authors also reviewed references of relevant studies.

STUDY SELECTION

Two authors reviewed studies evaluating the test characteristics of history, examination, widely used and available laboratory tests, and severity grading scales pertaining to envenomation by Crotalinae native to the Americas for analysis.[1] Authors included retrospective and prospective studies meeting all eligibility criteria.

DATA EXTRACTION AND SYNTHESIS

Two authors evaluated data from included studies and assessed methodological quality using the Rational Clinical Examination grading scale.[2] Reviewers assessed bias with the Quality Assessment of Diagnostic Accuracy Studies–2

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Results

Results of included studies.

Feature	Studies (Quality Level)	Sensitivity, % (95% CI)	Specificity, % (95% CI)	Positive LR (95% CI, I^2 [%])	Negative LR (95% CI, I^2 [%])
Time from bite to treatment ≥6 h	4 (3)	38 (14–69)	88 (83–92)	3.4 (1.1–64, 12)	0.69 (0.34–0.98, 33)
≤12 y	1 (3) 1 (4)	38 (23–56) 48 (30–67)	88 (79–94) 83 (70–91)	3.2 (1.5–7.1, NA) 2.9 (1.3–6.2, NA)	0.70 (0.52–0.94, NA) 0.63 (0.42–0.94, NA)
Large snake	3 (3) 3 (4)	66 (32–89) 19–92 (7–99)	88 (44–94) 64–100 (61–100)	3.1 (1.5–5.7, 31) 2.3–5.1 (0.3–90, NA)	0.45 (0.23–0.74, 0) 0.13–0.84 (0.01–1.85, NA)
Ptosis	1 (4) 1 (4)	100 (22–100) 100 (85–100)	78 (63–88) 32 (14–58)	3.8 (1.8–8.3, NA) 1.4 (1.0–2.1, NA)	0.21 (0.02–3.0, NA) 0.08 (0.01–0.14, NA)
Bite on digit	1 (3) 1 (4)	75 (54–88) 40 (31–49)	76 (74–77) 68 (65–71)	3.1 (2.4–4.0, NA) 1.3 (1.0–1.6, NA)	0.33 (0.16–0.68, NA) 0.88 (0.75–1.00, NA)
Bleeding distant to bite	1 (4)	22 (15–30)	92 (90–94)	2.8 (1.8–4.4, NA)	0.85 (0.77–0.94, NA)
Hypofibrinogenemia	1 (4)	46 (22–71)	91 (80–96)	5.1 (1.7–15)	0.60 (0.35–1.0)
Abnormal PT	1 (4)	96 (70–100)	63 (49–75)	2.6 (1.8–3.1)	0.07 (0.00–1.0)
Abnormal PTT	1 (4)	46 (22–71)	85 (73–92)	3.1 (1.2–7.5)	0.64 (0.37–1.1)
Thrombocytopenia	1 (4)	71 (43–89)	81 (68–89)	3.7 (1.9–7.3)	0.36 (0.15–0.88)

LR, Likelihood ratio; *NA*, not available; *PT*, prothrombin time; *PTT*, partial thromboplastin time.

standards and determined study quality level according to this assessment, with scores 1 to 4.[3] Studies graded level 1 were highest quality, with an independent blinded comparison of the index test and a valid reference standard with 200 consecutively enrolled patients. Studies graded level 4 were lowest quality, with a nonindependent comparison of the index test and reference standard. If an article evaluated more than one index test, the authors assessed the methodologic quality of each test. Authors resolved any disagreements through article review and discussion. They assessed envenomation severity according to systemic toxicity, tissue injury, and hematologic effects. Severe systemic toxicity was determined with comprehensive grading scales, severe tissue injury was defined as tissue necrosis, and hematologic effects were reported as recurrent, persistent, or late coagulopathy.[4-7] Authors calculated sensitivity, specificity, likelihood ratios, 95% confidence intervals (CIs), and pretest probability with random-effects measures. Heterogeneity was assessed with the I^2 statistic.

Authors included 17 studies comprising 5,915 patients from the Americas. Of these, 6 studies were graded level 3 and 11 were graded level 4. Only 4 studies were of sufficiently high quality to include in the meta-analysis. The most significant source of bias was from performance of the reference standard. Of included patients, 73.2% were male sex and 74% were adults. The prevalence of severe systemic envenomation was 14% (95% CI 9% to 21%), severe tissue injury prevalence was 14% (95% CI 12% to 16%), and severe hematologic effects occurred in 18% (95% CI 8% to 27%). Several findings from the history, physical examination, and laboratory assessment suggested severe snakebite envenomation (Table).

Commentary

Greater than 5 million people experience a bite from a venomous snake every year, and 9,000 of these bites occur in the United States, resulting in 5 to 10 deaths annually.[8-10] In the United States, 98% of these bites are from the *Crotalus*, *Sistrurus*, and *Agkistrodon* genera.[10] Snakebites can range from a dry, asymptomatic bite to severe envenomation with shock, hemorrhage, limb necrosis, organ failure, and death.[4,5] For simplicity, envenomation may result in 3 effects: tissue injury, hematologic abnormalities, and systemic effects.[4-7] Because of a variety of presentations and the rarity with which physicians will manage patients with snake envenomation, a clear understanding of the history, physical examination, and laboratory findings is vital to diagnose envenomation and treat with antivenom because patients often present to the emergency department for evaluation and management.[5,11] Antivenom, specifically Crotalidae polyvalent immune Fab (ovine), is derived from sheep serum and administered for progressive swelling, platelet count less than 100,000/mm^3, abnormal coagulation panel result, fibrinogen level less than 100 mg/dL, or systemic manifestations. The initial dose is 4 to 12 vials administered according to clinical judgment and severity, followed by recommendations for poison center consultation and repeated dosing if initial symptoms fail to improve.[11]

This systematic review and meta-analysis sought to identify findings associated with severe envenomation.[1] The most predictive features were time from envenomation to treatment greater than or equal to 6 hours, aged 12 years or younger, and bites from large (adult) snakes. Bites from *Crotalus* (rattlesnakes) were more frequently associated with severe systemic envenomation compared with bites from *Agkistrodon* (copperheads and cottonmouths). Ptosis was associated with severe envenomation and death, whereas the absence of ptosis was a good prognostic sign in cases of South American envenomation. One study found that initial hypofibrinogenemia, abnormal prothrombin time, abnormal partial thromboplastin time, and thrombocytopenia increased the likelihood of hematologic effects.[7] Results suggest that the absence of features from the history, examination, and laboratory results cannot definitively exclude envenomation, but it can decrease the likelihood of severe envenomation. Current guidelines recommend antivenom for both severe and nonsevere envenomations, but the quantity and timing of therapy depend on severity.[11]

The reported article has several limitations.[1] Included studies used a different reference standard for severe snakebite, which was based on which venom effect the individual study evaluated. Authors attempted to address this by grouping and reporting severity by

primary domains of injury, and they used consistent definitions within these groups when evaluating severity. Although 1 to 5 deaths occur in the United States every year from envenomation, possibly because of intravascular introduction of venom, this represents a small but important subset of envenomations, and authors of this article did not focus on these patients. Incorporation bias was present in the evaluation of test performance because severity grading scales evaluating systemic envenomation contained elements of the index test. There was also lack of generalizability to other snake types because this review evaluated only envenomation from Crotalinae genera. Venoms from other genera may result in different presentations, and factors associated with severity for these snakes likely differ. This analysis also did not assess a clinical or laboratory factor alone as a trigger for when to begin antivenom therapy.

According to this review's results, few clinical features can exclude severe snake envenomation, although several findings increase the likelihood of a severe bite. For patients with signs or symptoms of envenomation, clinicians should evaluate for features of severe envenomation, obtain suggested laboratory assessments, initiate antivenom therapy for symptomatic patients or those with laboratory-result abnormalities, and understand that severity of envenomation affects antivenom dose and duration. The literature would benefit from further data evaluating other snake species, findings in mild and moderate envenomations, and optimal timing of initiation of antivenom treatment.

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