Effect of Immune Response in the Pathophysiology of Snake Envenoming and Antivenom Treatment: A Scoping Review of Clinical Evidence

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Snake envenoming poses a significant public health challenge, especially in tropical regions. The toxin and non-toxin components of snake venoms trigger both innate and adaptive immune responses in victims possibly playing a role in severe envenoming outcomes. This scoping review aimed to consolidate existing literature on immune responses in snakebite envenoming and antivenom treatment, summarizing significant clinical evidence. JBI scoping review methodology group and five-step framework previously described by Arksey and O'Malley were followed. A three-step literature search for English-language articles that reported original data from 2000 to 2024 was conducted. The preliminary search identified relevant keywords. An advanced search was performed across PubMed, EMBASE, Scopus, Web of Science and Cochrane Library, using a predefined search strategy, followed by a citation search to identify relevant grey literature. Of 19,551 records retrieved, 8,679 were manually screened after removing duplicates. After excluding irrelevant records, 17 abstracts were selected for full-text review, and 13 met the eligibility criteria. One additional article was retrieved from grey literature, totaling 14 studies on immune response in snake envenoming (local envenoming-3; systemic envenoming-4; local and systemic-5; adverse effect to antivenom-2) involving 981 patients. Only eight verified case authentication and snake authentication (*Daboia russelii*, *Bothrops atrox*, *Echis carinatus sochureki*, *Agkistrodon contortrix*, *Protobothrops mucrosquamatus*, *Viridovipera stejnegeri*, and *Naja atra*). Some study designs (n=4) could not distinguish whether immune response changes were due to antivenom or natural history. Most studies assessed the responses of TNF-α, IFN-γ, IL-1β, IL-2, IL-4, IL-6, IL-10, IL-17A, CCL-2/MCP-1, CCL-5/RANTES, CXCL-8/IL-8, CXCL-9/MIG, and CXCL-10/IP-10 in relation to local tissue complications, coagulopathy, kidney injury, and antivenom reactions. Overall, most studies showed a rise in the inflammatory mediators IL-1β, IL-6, and IL-10 following snake envenoming, compared to the control group. However, reduction in IL-10 was reported in two studies that examined severe envenoming. Higher concentrations of CXCL-8/IL-8 were associated with local effects, acute kidney injury, secondary infections, and antivenom reactions. Existing clinical studies indicate that snake envenoming causes an elevation of pro-inflammatory cytokines; IL-1β, IL-6 and anti-inflammatory cytokine IL-10. However, as envenoming severity increases, IL-10 levels appear to decrease. CXCL-8/IL-8 may also contribute to the development of severe envenoming outcomes.

Keywords: Immune response, snakebite, snake envenoming, snake venom, antivenom