

Bacterial Infections Associated with Viperidae Snakebites in Children: A 14-Year Experience at the Hospital Nacional de Niños de Costa Rica†

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Abstract. Secondary bacterial infections following Viperidae snakebite envenomation in children are common. Among 75 patients admitted because of snakebites at the only pediatric hospital in Costa Rica, 16 (21.3%) had a culture-confirmed secondary bacterial infection. *Morganella morganii* (37.5%), *Aeromonas hydrophila* (31.2%), and *Providencia rettgeri* (18.7%) were the most common pathogens. Empiric prophylaxis is still recommended and should be based on local etiological agents and antimicrobial susceptibilities.

Worldwide, around two million cases of snakebite accidents occur annually in the general population, with more than 100,000 associated deaths.¹ Because of the topography and weather factors, a considerable amount of snakebite accidents occur in Latin America, with significant associated morbidity mainly due to envenomation-associated problems, delayed access to medical care, and secondary wound infections.^{2,3}

Infections associated with snakebites are a common complication in these patients,⁴ especially those occurring in skin and soft tissues. In the early 1980s, it was described that snake fangs contain aerobic and anaerobic bacteria, reaching 3×10^{24} UCF/mL pathogens in some studies.⁵ This observation was confirmed in other studies, documenting that oral microbiota of snakes comprise a wide range of aerobic and anaerobic microorganisms, including *Enterobacteriaceae* (*Morganella* spp. and *Escherichia coli*), *Streptococcus* spp., and *Aeromonas* spp. However, the predominant microorganisms change according to different geographic regions and environmental conditions.⁶ The main etiologic agents of primary and nosocomial infections include *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Aeromonas hydrophila*.⁴

Our main objective was to describe the microbiological aspects of bacterial infections associated with snakebite accidents due to the Viperidae family at our institution.

We performed a retrospective descriptive study of children who suffered Viperidae snakebite accidents and were admitted and treated at the Hospital Nacional de Niños “Dr. Carlos Sáenz Herrera,” Centro de Ciencias Médicas, Caja Costarricense de Seguro Social, the only national pediatric tertiary referral academic hospital of Costa Rica. Most patients were transferred from primary and secondary level care centers. Although general information about initial management at the emergency room was collected from the medical charts of all patients, we focused our analysis on the type of infections and the microbiological data of the microorganisms detected by

bacterial culture from skin, soft tissues, joints, and blood. An analysis of the antibiotic treatment schedules that were prescribed was also made. We analyzed patients admitted from January 1, 2001, to December 31, 2014. Patients were identified by a discharge diagnosis of snake envenomation (ICD-11 code: XM4MC9).

For statistical data analysis, we used EpiData 3.1 (Epidata Association, Enghavevej, Odense, Denmark), Excel 14.5.8 (Microsoft Corporation, Redmond, WA), and Prism 6 (Graph-Pad Software, San Diego, CA). This study was approved by the Bioethical and Research Committee of our institution, project CLOBI-HNN-001-2015.

We analyzed 75 children hospitalized with snakebite envenomation during the 14-year period. Fifty (66.6%) patients (pts) were male, and medium age at admission was 8.8 years (range 5.6–11.8 years). Sixteen (21.3%) pts had a secondary associated bacterial infection (Table 1), and are the subjects of the current analysis. Of these, nine (6.2%) had a polymicrobial infection (defined as > 1 microorganism detected). Thirteen (81%) pts were male; medium age was 8.2 years (range 1.11–12.7 years). All pts received medical attention within the first 24 hours, of whom 10 (62.5%) occurred during the first 4 hours after the snakebite, three (18.7%) pts between 4 and 8 hours, and three (18.7%) pts after 8 hours. All patients received polyvalent anti-Viperidae antivenom, produced in Costa Rica by the Instituto Clodomiro Picado as a polyvalent antivenom (anti-Bothrops, anti-Crotalus, and anti-Lachesis venom).

The anatomical distribution of the site of snakebites was as follows: lower extremities, nine (56%) pts; upper extremities, six (37.5%); and abdomen, one patient (6.2%). Regarding the clinical presentation, 14 (87.5%) pts developed soft tissue abscesses; necrotizing fasciitis, septicemia, and septic arthritis occurred in one patient each (6.3%). Overall, six children developed infections caused by *Morganella morganii* (37.5%); *Aeromonas hydrophila*, five (31.2%); and *Providencia rettgeri*, three (18.7%), these three being the most common pathogens isolated. All 16 patients received prophylactic antibiotics (defined as treatment initiated on admission in the emergency room), and they were continued according to the infectious diseases or treating physicians' recommendations. All patients required intravenous combined antibiotic therapy with clindamycin (or penicillin) plus an aminoglycoside (or third-generation cephalosporin). The initial selection and length of antibiotics were modified and tailored as needed according to the susceptibility test report and interpretation, presence or

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TABLE 1
Etiologic agents and clinical manifestations of infections in children bitten by venomous snakes

Patient	Age (months)	Isolated microorganism(s)	Clinical manifestations	Microorganism and drug resistance characteristics documented
1	131	<i>Klebsiella pneumoniae</i> , <i>Candida albicans</i>	Soft tissue abscesses	<i>K. pneumoniae</i> ESBL + <i>C. albicans</i> : no resistance
2	107	<i>K. pneumoniae</i> , <i>Staphylococcus epidermidis</i>	Soft tissue abscesses	<i>K. pneumoniae</i> ESBL + <i>S. epidermidis</i> : no antibiogram available
3	114	<i>Morganella morganii</i> , <i>Pasteurella pneumotropica</i>	Soft tissue abscesses	<i>M. morganii</i> : ampicillin and first-generation cephalosporin resistance; <i>P. pneumotropica</i> : no antibiotic resistance
4	92	<i>M. morganii</i> , <i>Providencia rettgeri</i> , <i>Stenotrophomonas maltophilia</i>	Soft tissue abscesses	No antibiotic resistance
5	107	<i>M. morganii</i>	Septicemia and soft tissue abscesses	No antibiotic resistance
6	98	<i>M. morganii</i>	Soft tissue abscesses	No antibiotic resistance
7	112	<i>P. rettgeri</i>	Soft tissue abscesses	Ampicillin resistance
8	151	<i>P. rettgeri</i>	Soft tissue abscesses	First-generation cephalosporin and gentamicin resistance
9	148	<i>Enterococcus gallinarum</i>	Soft tissue abscesses	Ciprofloxacin, erythromycin, and vancomycin resistance
10	32	<i>Aeromonas hydrophila</i> , <i>Enterococcus casseliflavus</i>	Soft tissue abscesses	<i>A. hydrophila</i> : no antibiotic resistance; <i>E. casseliflavus</i> : clindamycin resistance
11	133	<i>Proteus vulgaris</i> , <i>A. hydrophila</i>	Soft tissue abscesses	<i>P. vulgaris</i> : ampicillin resistance; <i>A. hydrophila</i> : ampicillin and first-generation cephalosporin resistance
12	72	<i>A. hydrophila</i>	Soft tissue abscesses	No antibiotic resistance
13	114	<i>A. hydrophila</i> , <i>M. morganii</i>	Soft tissue abscesses	No antibiotic resistance
14	72	<i>A. hydrophila</i> , <i>M. morganii</i>	Septic arthritis	No antibiotic resistance
15	76	<i>Ochrobactrum anthropi</i>	Soft tissue abscesses	No antibiotic resistance
16	130	<i>Pseudomonas aeruginosa</i> , <i>Staphylococcus aureus</i>	Necrotizing fasciitis	<i>P. aeruginosa</i> : no antibiotic resistance; <i>S. aureus</i> : methicillin resistance

absence of venom-induced acute tubular necrosis, and severity of the infections, among other criteria.

Other complications that were documented included compartmental syndrome, 13 (81%) pts; mucosal bleeding and serum sickness, one patient (6.2%); and antivenom-related anaphylaxis, one patient (6.2%). Thirteen (81.2%) pts had long-term sequelae, one (6.2%) needed amputation of compromised fingers, six (37.5%) needed skin grafts, six (37.5%) developed functional limited mobility, six had deforming scars, and two (12.5%) had deformity of the affected limb. No deaths were documented during this period.

In our study, the most common microorganisms isolated were those from the normal oral cavity flora of snakes. Less frequently, common human skin pathogens were also an important cause of infection in our population, comprising predominantly nosocomial infections. These findings are supported by previous literature describing similar pathogen distribution.⁷⁻⁹ Two previous local studies from our institution described the microbiologic aspects among snakebite accidents, with *M. morganii* and *Aeromonas hydrophila* being the two main pathogens detected.^{4,10} Therefore, no important changes in the etiologic agents were documented in our study. Information regarding antibiotic resistance in other series of snakebite patients was not available in previous Costa Rican publications.

Early complications reported in the literature, such as septic arthritis, necrotizing fasciitis, or septicemia, are uncommon in most pediatric reports. Nevertheless, these should be suspected in cases of severe envenomation or in patients who have delayed medical care (defined as more than 4 hours after the event). Although most studies describe soft tissue infections as the most common complications of Viperidae snakebite accidents,¹⁰ severe complications such as the ones

described in our study are associated with prolonged hospitalizations, as recurrent surgical procedures and prolonged antibiotic courses are often needed. All our patients were categorized as having moderate or severe envenomation, where tissue compromise and extent of tissue damage are characteristic.^{1,11}

Virulence factors of some of the most common bacteria associated with snakebite must be considered when treating snakebite patients to anticipate infectious complications.⁷ Some articles recommend the use of prophylactic antibiotics when there are necrotic tissue of clinically obvious wound infection,^{1,6} whereas on the other hand, some local and international literature supports the use of prophylactic antibiotics in every snakebite patient.^{3,4} Although all of our patients received antimicrobial prophylaxis, almost one-fourth developed infection at some point during the hospitalization. A possible explanation for this finding is that some of these children had delayed medical attention, and this fact could have contributed to the infection process in them.^{3,4} Other proposed contributing factors include tissue damage and necrosis produced by the venom and released toxins. There are animal studies demonstrating that tissue damage caused by venom and cytokine release can play a significant role in promoting bacterial infection.¹¹ Further investigations regarding the occurrence of infection despite prophylactic antibiotic treatment is needed because this phenomenon has been described in other centers and supports the recommendation of antibiotic prophylaxis.^{2,7}

Bothrops spp. snake venom induces clinical and pathophysiological alterations similar to acute trauma, with release of proinflammatory cytokines that cause tissue damage and increase infection risk. The use of antibiotic prophylaxis effectively against aerobic and histotoxic anaerobic organisms

is now recommended, but the use of early antivenom (in the first 4 hours after the event) is equally important to prevent bacterial superinfection, probably because antivenom reduces the extent of local tissue damage, which is a contributing factor of infection.¹¹

The use of prophylactic antibiotics in these patients has been controversial.⁶ In the early 1980s, in a local Costa Rican study, researchers documented that venom from *Bothrops asper* snakes was sterile, but the faucets contained a large amount of anaerobic and aerobic bacteria.⁶ Our data show there is a high rate of polymicrobial infections in this population, reinforcing the recommendation from other studies of initial empiric combined intravenous antibiotic therapy against Gram-positive, Gram-negative, and anaerobic bacteria.^{2,3,10} Recommendations should be used with caution as national and international supporting publications in this area are scarce and not clear.^{1,4,7,8,10}

Most of our isolates were susceptible to aminoglycosides, clindamycin, or penicillin (Table 1), supporting the combination of penicillin or clindamycin with an aminoglycoside as the empirical treatment.^{3,7} Although suggesting antibiotic prophylaxis was not the intention of this study and our sample is small, the use of antimicrobial prophylaxis against aerobic and anaerobic pathogens is recommended in some reports.

No deaths were documented during this study period. Sequelae were high in our study group, supporting previous data that infection is a risk factor for further complications in these patients.^{10–12}

We acknowledge the limitations of our study. First is the inherent limitation of a retrospective descriptive study. As a referral hospital, we do not admit all pediatric patients with snakebite accidents; therefore, our findings are not representative of the whole country. Second, although this was a 14-year study, our sample was small and so management recommendations cannot be generalized to all populations. Third, empiric initial antibiotic therapy varied across different referral centers.

Wound infections are common among children with Viperidae snakebite accidents, with *M. morgani*, *A. hydrophila*, and *P. rettgeri* being the three most common responsible pathogens. The use of prophylactic antibiotics continues to be an important aspect in the management of these patients; however, prospective multicenter studies involving more patients and addressing their role are needed. In the meantime, empiric prophylaxis is still recommended and should be based on local etiological agents and antimicrobial susceptibilities.

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