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Incidence and Risk Factors for Wound Infections after *Trimeresurus stejnegeri* Snakebites in Taiwan

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Abstract. Snakebite envenomation is a neglected tropical disease. Taiwan, with its subtropical and Southeast Asian environment, provides suitable habitat for several venomous snake species. *Trimeresurus stejnegeri*, an arboreal pit viper, is the most common cause of venomous snakebite in Taiwan. *Trimeresurus stejnegeri* envenomation can cause local swelling, occasional ecchymosis, and wound infection. The primary treatment of *T. stejnegeri* envenomation is the binary antivenom, vacuum freeze-dried F(ab′)2 fragments of equine antibodies, against *T. stejnegeri* and *Protobothrops mucrosquamatus*. This study aimed to analyze the incidence of post-envenomation wound infections caused by *T. stejnegeri* based on data collected over a decade from institutions affiliated with the Chang Gung Memorial Hospital in Taiwan. A total of 254 patients were enrolled in this study. Clinical and laboratory data, treatment information, and patient outcomes were extracted from electronic medical records. Wound infection was associated with delay in antivenom initiation (adjusted odds ratio: 3.987; 95% CI: 1.406–11.302). The infection rates were 20.5%, 12.5%, 31.3%, and 48.1% for antivenom administration within 2 hours, 2–4 hours, 4–6 hours, and $>$ 6 hours, respectively. Therefore, early initiation of antivenom treatment (within 6 hours) is recommended. *Morganella morganii* was cultured from wounds of the patients, whereas *Enterobacter cloacae* and *Enterococcus faecalis* were cultured from both the oral cavity of snakes and the wounds of the patients. For post-envenomation patients who develop a local infection, empiric antibiotics such as third-generation cephalosporins, quinolones, and piperacillin/tazobactam are recommended because snakebite wound infections are often polymicrobial in nature.

INTRODUCTION

Snakebite envenomation is a neglected tropical disease that affects approximately 2.7 million individuals and causes 81,000–138,000 deaths every year according to the WHO.[1] Located in a subtropical and Southeast Asian environment, Taiwan has pleasant climatic conditions and various terrains, providing a favorable environment for several venomous snake species,[2] including mainly *Trimeresurus stejnegeri*,[3,4] *Protobothrops mucrosquamatus*,[5,6] *Deinagkistrodon acutus*,[7,8] *Bungarus multicinctus*,[9,10] *Naja atra*,[11,12] *Daboia siamensis*,[13,14] *Ovophis makazayazaya*,[15,16] and *Trimeresurus gracilis*.[17,18]

Trimeresurus stejnegeri, belonging to the Viperidae family, is one of most common causes of venomous snakebites in Taiwan.[19] *Trimeresurus stejnegeri* envenomation usually leads to local swelling, edema, and occasional ecchymosis; however, systemic syndrome characterized by severe bleeding or coagulopathy is rare.[20,21] Chiang et al.[22] discussed the risk factors for wound necrosis after a *T. stejnegeri* bite.

The main treatment of *T. stejnegeri* envenomation is the binary antivenom, vacuum freeze-dried F(ab′)2 fragments of equine antibodies, against *T. stejnegeri* and *P. mucrosquamatus*.[20] Retrospective studies suggest that patients should start with 1–2 vials of antivenom after envenomation.[19,23,24] Although there is a relatively low risk of surgery, a small number of patients suffer from severe limb tenderness or hemorrhagic bullae formation, and surgical interventions, including wound debridement, fasciotomy, and skin grafting, may be necessary.[25–27]

Previous studies have reported that the rate of wound infection was 11.4–22.5% among individuals bitten by *T. stejnegeri*.[22,28] However, relevant research on the risk factors of wound infection, identification and comparison of bacteria cultured from wounds and snake oral cavities, and antibiotic susceptibility of snakebite wound infections is still insufficient. Thus, our study aimed to analyze post-envenomation wound infections caused by *T. stejnegeri* based on a decade of experience in Taiwan.

MATERIALS AND METHODS

Study setting and data collection. We conducted chart reviews at Chang Gung Memorial Hospital institutions spanning from northern to southern Taiwan, including branches in Keelung, Linkou, Chiayi, and Kaohsiung. We searched patients using the following keywords: "binary antivenom of *T. stejnegeri* and *Protobothrops mucrosquamatus*," "*T. stejnegeri* bites," or "snakebites." Patients with *T. stejnegeri* snakebites who were administered antivenom at the same visit between January 2011 and December 2020 were identified.

"Definite cases" included patients having envenomation signs and symptoms or fang marks (if any) and for whom the snake could be physically identified. "Suspected cases" included patients having envenomation symptoms or fang marks (if any) and for whom there was only a pictorial identification of the snake. As defined by physicians, "clinical cases" included patients with wounds and histories resembling those of *T. stejnegeri* snakebite cases.[5,11] This study enrolled patients with definite cases and suspected cases who received antivenom and excluded clinical cases and dry bite cases. A total of 254 patients were enrolled after a thorough review of their medical records by the corresponding author. Subsequently, the first author double-checked the medical history of emergency visits and hospital admissions.

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Measurements. One vial (20 mL) of antivenom was diluted with 0.9% sodium chloride (200–300 mL) for reconstitution and then infused intravenously for 30 minutes. For the skin test, diluted antivenom (0.1 mL of 1:100) was injected intradermally into the forearm. Local induration or redness over the injected skin or systemic allergies that occurred within 30 minutes after antivenom administration were defined as a positive skin test.[29,30] The clinical characteristics, laboratory data, treatments, and clinical outcomes of the patients were extracted from electronic medical records.

Wound infections were defined as those meeting any of the following criteria: 1) increased or sustained pain, erythema, edema, purulence, bad odor, or nonhealing of the wound or at the bite site with diagnosis of cellulitis, subcutaneous abscess, osteomyelitis, or sepsis by physicians or 2) positive wound cultures.[20,22]

Anderson et al.[31] discussed the benefits of early antivenom injections and defined patients receiving antivenom at 5.47 hours after snakebite as "delayed dosing." In this study, "delayed initiation of antivenom" was defined as over 6 hours from snakebites to initiation of the first antivenom administration.

Antivenom reactions were defined as skin rashes, itching, eyelid swelling, redness of eyes, wheezing, or bronchospasm within 3 hours after antivenom administration, and these patients received antihistamine, steroid, or a bronchodilator.[32–34] Severe antivenom reactions were defined as 1) hypotension and treatment with fluid resuscitation or epinephrine injection or 2) respiratory failure with subsequent intubation due to antivenom reactions.[34,35]

Data analysis. Continuous variables of age, medication doses, triage vital signs, laboratory data, antivenom doses, time from bite to antivenom, and length of hospital stay are presented as median with interquartile range. Categorical data are presented as number and percentage. The Mann-Whitney *U* test, one-way analysis of variance, χ^2 test, *Z* test with Bonferroni correction, and Fisher's exact test were used to analyze the data.

Binary logistic regression was used to adjust for potential confounding factors of the association between variables and wound infection. Model confounders were adjusted for age, male sex, hypertension, diabetes mellitus, liver cirrhosis, end-stage renal disease, malignancy, envenomation location, hospital location, and transfer to another hospital. Adjusted odds ratios (aORs) and corresponding 95% CIs were used to estimate the association. Results were considered statistically significant for two-tailed tests at $P < 0.05$. All statistical analyses were performed using the IBM Statistical Package for the Social Sciences for Windows (version 22.0; released 2013; IBM Corp., Armonk, NY).

RESULTS

Characteristics and laboratory data. Of the 254 patients bitten by *T. stejnegeri*, 65 developed wound infections and 189 had no wound infection (Table 1). No significant differences were observed in age, sex, underlying diseases, or vital signs at the time of triage. The bites occurred on a limb in most cases; only three patients (1.6%) were bitten on their

TABLE 1
Clinical character and laboratory data of patients with *T. stejnegeri* snakebites

Characteristics	Snakebite envenomed wounds		*P* value
	Infection (*N* = 65)	No infection (*N* = 189)	
Age (years)	60 (53–69)	60 (49–70)	0.934
Male sex	39 (60%)	136 (72%)	0.072
Hypertension	19 (29.2%)	41 (21.7%)	0.217
Diabetes mellitus	4 (6.2%)	18 (9.5%)	0.405
Liver cirrhosis	5 (7.7%)	9 (4.8%)	0.358
End-stage renal disease	0 (0%)	3 (1.6%)	0.572
Malignancy	4 (6.2%)	4 (2.1%)	0.209
Hospital location			
Keelung	9 (13.8%)	52 (27.5%)	
Taipei and Linkou	23 (35.4%)	87 (46%)	
Chiayi	7 (10.8%)	2 (1.1%)	< 0.001
Kaohsiung	26 (40%)	48 (25.4%)	
Fever	6 (9.2%)	6 (3.2%)	0.082
Heart rate at triage (beats per minute)	85 (75–106)	84 (75–99)	0.455
Mean BP at triage (mm Hg)	101 (124.3–109.3)	111 (101–124.3)	0.476
Envenomation location			
Upper extremity	38 (58.5%)	125 (66.1%)	
Lower extremity	27 (41.5%)	61 (32.3%)	0.263
Trunk or other	0 (0%)	3 (1.6%)	
Transferred from other hospitals	21 (32.3%)	28 (14.8%)	0.002
Laboratory data			
White blood cells (1,000/μL)	8.7 (6.35–11.6)	7.4 (5.9–8.9)	0.006
Segment (%)	67 (55.9–79.2)	61.8 (54.3–71.7)	0.036
Hemoglobin (g/dL)	13.8 (12.9–15.1)	14.4 (13.5–15.3)	0.016
Platelets (1,000/μL)	212 (178–269)	219 (183–255)	0.791
Prothrombin time (seconds)	11.1 (10.5–11.9)	10.9 (10.4–11.7)	0.386
aPTT (seconds)	27.4 (25.9–29.1)	27.6 (26.3–29.3)	0.343
Creatinine (mg/dL)	0.78 (0.63–1)	0.84 (0.72–1)	0.183
Alanine transaminase (U/L)	19 (14–30)	20 (15–29)	0.427
C-reactive protein (mg/L)	1.8 (0.6–10.7)	1.35 (0.5–2.43)	0.124
Creatine phosphokinase (U/L)	153 (87–302.5)	171.5 (123–257.5)	0.824
D-dimer (mg/L)	0.64 (0.439–1.292)	0.516 (0.265–1.098)	0.387

aPTT = activated partial thromboplastin time; BP = blood pressure; *T. stejnegeri* = *Trimeresurus stejnegeri*. Data are presented as number (percentage) or median (interquartile range: 25–75%).

TABLE 2
Treatment and outcome of patients with *T. stejnegeri* snakebites

Treatment and Outcomes	Snakebite envenomed wounds		*P* value
	Infection ($N = 65$)	No infection ($N = 189$)	
Performed antivenom skin tests	50 (76.9%)	154 (81.5%)	0.425
Negative	48/50 (96%)	145/154 (94.2%)	1.000
Positive	2/50 (4%)	9/154 (5.8%)	–
Antivenom reactions	7 (10.8%)	23 (12.2%)	0.763
Severe antivenom reaction	1 (1.5%)	0 (0%)	0.256
Initial antivenom dose (vials)	1 (1–1)	1 (1–1)	0.353
Bite to antivenom (hours)	2.3 (1.17–6.84)	1.9 (1.16–2.62)	0.186
< 2 hours*	23/48 (47.9%)	89/163 (54.6%)	
2–4 hours*	7/48 (14.6%)	49/163 (30.1%)	
4–6 hours*	5/48 (10.4%)	11/163 (6.7%)	0.003
> 6 hours*	13/48 (27.1%)	14/163 (8.6%)	
Total antivenom dose (vials)	2 (1–4)	2 (1–3)	0.007
Performed bacteria culture	27 (41.5%)	10 (5.3%)	< 0.001
Culture positive	4 (6.2%)	0 (0%)	0.284
Oral antibiotics	56 (86.2%)	132 (69.8%)	0.010
Penicillin class	42 (64.6%)	95 (50.3%)	0.045
Cephalosporin class	15 (23.1%)	37 (19.6%)	0.546
Quinolone class	0 (0%)	1 (0.5%)	1.000
Other classes	2 (3.1%)	2 (1.1%)	0.259
Intravenous antibiotics	58 (89.2%)	74 (39.2%)	< 0.001
Penicillin class	46 (70.8%)	44 (23.3%)	< 0.001
Cephalosporin class	17 (26.2%)	28 (14.8%)	0.039
Aminoglycoside class	10 (15.4%)	11 (5.8%)	0.016
Quinolone class	0 (0%)	1 (0.5%)	1.000
Other classes	2 (3.1%)	5 (2.6%)	1.000
Admission	52 (80%)	59 (31.2%)	< 0.001
Hospital length of stay	4.4 (2.57–7.03)	1 (0.4–2.65)	< 0.001
Surgery	6 (9.2%)	8 (4.2%)	0.203
Debridement	6 (9.2%)	5 (2.6%)	0.035
Fasciotomy	5 (7.7%)	7 (3.7%)	0.191
Grafting	2 (3.1%)	0 (0%)	0.065

T. stejnegeri = *Trimeresurus stejnegeri*. Data are presented as number (percentage) or median (interquartile range: 25–75%).
* A total of 48 and 163 patients had recorded their first antivenom time in the infection and no infection groups, respectively.

trunk or face, which did not lead to wound infection. Patients transferred from other hospitals showed a significant difference in the rate of wound infections (32.3% versus 14.8%, $P = 0.002$). There were no significant differences in continuous variables of laboratory data except white blood cells, segment, and hemoglobin (median [Q1–Q3], 8.7 [6.35–11.6] versus 7.4 [5.9–8.9], $P = 0.006$; 67 [55.9–79.2] versus 61.8 [54.3–71.7], $P = 0.036$; and 13.8 [12.9–15.1] versus 14.4 [13.5–15.3], $P = 0.016$, respectively). In addition, to avoid numerical deviation, we used the cutoff levels of D-dimer (> 0.55 mg/L fibrinogen equivalent units) and creatine phosphokinase (CPK > 1,000 U/L) for statistical analysis. However, there were still no significant differences in rate of wound infections and elevated D-dimer or CPK levels (9.2% versus 7.9%, $P = 0.497$; 1.5% versus 1.1%, $P = 1.000$).

Treatment and outcomes. A comparison of the risk factors, treatments, and outcomes for wound infection due to snakebites is summarized in Table 2. In all enrolled cases, 80.3% of patients underwent an allergy skin test. In addition, the positive skin test rate was 5.4%, with one of the patients progressing to a severe allergic reaction. Forty-three patients were excluded because the exact timing of venom administration was unclear. A delay in the initiation of antivenom administration (> 6 hours) was associated with a higher wound infection rate (48.1% versus 19.0%, respectively, $P = 0.003$). We then conducted the Z test with Bonferroni correction for < 2 hours, 2–4 hours, 4–6 hours, and more than 6 hours (Figure 1), which revealed statistically significant differences between the < 2 hour and 2–4 hour groups and the over 6 hour group, whereas there were no statistically significant differences between the 4–6 hour group and the other groups. Most patients were administered either oral or intravenous antibiotics in the emergency department, with penicillin being the main choice. In the penicillin class, oral agents included amoxicillin (2), amoxicillin/clavulanic acid (117), and dicloxacillin (20); and intravenous agents included oxacillin (38), amoxicillin-clavulanic acid (54), ampicillin-sulbactam (8), and piperacillin-tazobactam (1). Relatively, in the cephalosporin

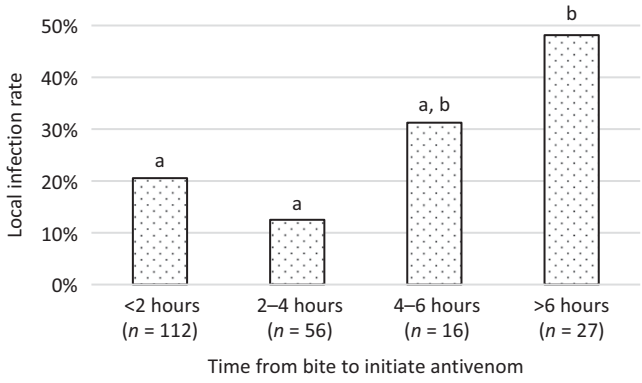

FIGURE 1. Infection rate at different times from bite to antivenom administration. The letters a and b indicate group differences based on the Z test with Bonferroni correction ($P = 0.003$).

TABLE 3
Association of wound infection with delay in antivenom injection, antivenom doses, and surgery ($N = 201$)

Variables	aOR	95% CI
Total antivenom dose (vials)	1.385	1.105–1.736
Delay in initiated antivenom (> 6 hours)	3.987	1.406–11.302
Surgery	0.826	0.13–5.265

aOR = adjusted odds ratio. Confounders of the model are adjusted for age, male sex, hypertension, diabetes mellitus, liver cirrhosis, end-stage renal disease, malignancy, envenomation location, hospital location, and transfer from other hospital.

class, oral agents included cefadroxil (39), cefuroxime (49), and cefixime (1), whereas intravenous agents included cefazolin (40), cefuroxime (1), ceftriaxone (8), and ceftazidime (2). After adjustment for potential confounding factors using logistic regression analysis, total antivenom dose (aOR: 1.385; 95% CI: 1.105–1.736) and delayed initiation of antivenom administration (aOR: 3.987; 95% CI: 1.406–11.302) were still associated with local infection (Table 3).

Patients with wound infections exhibited higher hospitalization rates, longer lengths of stay, and increased surgical rates. Surgical indications included wound infection or impending acute compartment syndrome in 14 patients. No cases of amputation or mortality were observed. Table 4 shows the comparison of individual clinical manifestations, antibiotic use before surgery, surgery type, time from bite to surgery, length of hospital stay, and bacterial culture results. A total of 37 patients underwent a culture test, and four tested positive. Positive bacterial cultures, including five organisms, were observed in three of the 14 specimens. In a previous study,[36] we compared the antibiotic susceptibility of these organisms and bacterial flora of the snake oral cavity (Table 5).

DISCUSSION

Wound infection caused by a *T. stejnegeri* bite is probably due to the cytotoxic effects of venom phospholipase A_2 and metalloproteinases injected into the tissues of the patients. Phospholipase A_2 exhibits various toxic and pharmacological effects, including neurotoxic, myotoxic, hemolytic, proinflammatory, anticoagulant, cytotoxic, and bactericidal activities.[37,38] The oral cavity and skin commensals of snakes are prone to colonizing the wound at an opportune time owing to tissue damage or necrosis.[22] It appears that the bacterial flora of the oral cavity of snakes is similar to that of the infected snakebite wounds. *Morganella morganii* and *Enterococcus* spp. were pathogens frequently isolated from the oral cavity of snakes by Chen et al.[39] The bacteria in infected wounds are compatible with the oral bacterial flora of snakes; for example, *E. faecalis* is the most common aerobic gram-positive organism in the oral cavity of *T. stejnegeri.*

There are many traditional first aid strategies for snakebites, such as topical herbs, ice packing, wound incision, and venom suction; however, there is insufficient evidence of their efficacy. Previous studies reported that cold packing diminishes tissue perfusion and causes wound necrosis.[22,40] Antivenom is the only effective and proven treatment of systemic snakebite envenomation and has been known to save victims of snakebites in the last hundred years.[34,41] The Taiwan Poison Control Center suggests that 1–2 vials of bivalent freeze-dried hemorrhagic (FH) antivenom should be administered as an initial dose.[42] Lin et al.[20] recommended that a higher dose of antivenom should be administered if rapid limb swelling (e.g., progressing across the other joint) occurs within 6 hours. In our study, the median total dose of FH antivenom was two vials. Of the study group, 27 patients (12.8%) received delayed antivenom treatment (> 6 hours), leading to a higher rate of wound infections. Experts may assume that a specific antivenom neutralizes the venom and accelerates recovery, but further research is needed to explore the direct mechanism of the association between early antivenom administration and reduced incidence of certain pathological effects.[22] On the other hand, we subdivided patients who received early initiated antivenom into three groups (< 2 hours, 2–4 hours, and 4–6 hours) and found that patients who were administered antivenom earlier than 2 hours had a higher infection rate than those who were injected in 2–4 hours. We speculated that this group of patients was brought to the emergency department and immediately received specific antivenom because they suffered from a critical bite injury or severe limb swelling and had a relatively high risk of infection. In patients referred from other hospitals, a higher rate of wound infection was observed. This could potentially be attributed to the delayed administration of antivenom owing to the unavailability of appropriate snake antivenom at the initial local hospital or the critical condition of the patients themselves.

C-reactive protein (CRP) is a widely known biomarker that is significantly correlated with bacterial infections or inflammation.[43] However, there were no significant differences in continuous variables between the two groups. The reason for this may be that we only collected data on the initial CRP levels upon arrival at the emergency department. In future studies, the CRP trends of patients at different stages after hospitalization should be tracked to analyze the correlation between CPR and wound infections.

Anaphylactic reactions to snake antivenoms can range from mild to life-threatening skin rashes.[44] In our study, one patient experienced a severe allergic reaction, but all allergic symptoms were relieved after a 0.5-mg epinephrine injection via the intramuscular route. In many Asian countries, most physicians perform the antivenom skin test according to the manufacturer's instructions and legal obligations unless the patients refuse.[11,35,45] However, irrespective of the skin test results, physicians should administer antivenom for snakebites.[29,35] According to WHO guidelines, the use of an antivenom skin test is discouraged.[34] Previous studies have reported a low skin screen test sensitivity of 17.5%, making it unsuitable as a screening test, and the actual antivenom allergic reaction rate was only 1.25%.[33] Consequently, one of the primary emphases of this study is that skin testing is unnecessary.

In our study, we found lower infection rates in northern cities (Linkou and Keelung) than in southern cities (Chiayi and Kaohsiung) of Taiwan. This may be because hospitals in northern Taiwan are relatively dense, and patients can visit clinics or hospitals for medical treatment without any delays. Second, most southerners live in the countryside and make a living through farming. Snake-infested areas are more common in the wild habitat, and it is difficult to distinguish between venomous and nonvenomous snakes. After being bitten by a snake, individuals often ignore it and observe it only when back home. Third, there is no accurate set of clinical criteria to define snakebite infection, and some physicians require positive bacterial cultures for diagnosis of

TABLE 4
Bacteria culture and characters of patients who underwent surgery

Case number	Hospital location	Bitten part	Wound manifestations	Antibiotic before surgery	Surgical types	Bite to surgery	Wound infection	HLOS	Bacterial culture
1	Keelung	Left ankle	Progressive swelling and ischemic change	Cefazolin and gentamicin	Debridement and fasciotomy	0.25 day	Yes	17.5 days	*E. cloacae* and *C. jeikeium*
2	Keelung	Left fifth finger	Coldness and cyanosis	Oxacillin	Fasciotomy	1 day	No	8.7 days	Not performed
3	Linkou	Left dorsal foot	Blister formation with numbness	Cefazolin and gentamicin	Debridement, fasciotomy, and flap	1 day	No	11.1 days	No growth
4	Linkou	Right hand	Progressive swelling, local tenderness, and numbness	Cefazolin	Debridement and fasciotomy	0.25 day	No	4.7 days	Not performed
5	Linkou	Right fifth finger	Progressive swelling, distal numbness, and capillary refill time: 3 seconds	Ceftriaxone	Debridement, fasciotomy, and flap	0.5 day	No	8.9 days	Not performed
6	Chiayi	Right heel	Bullae formation, necrotic skin, and pus discharge	Ceftriaxone and metronidazole	Debridement and grafting	7 days	Yes	47.0 days	*M. morganii* and *E. faecalis*
7	Chiayi	Right foot	Progressive swelling, bullae, ecchymosis, and necrosis	Cefazolin	Debridement, fasciotomy, and flap	3 days	Yes	49.6 days	*S. putrefaciens*, *E. faecalis*, and *M. morganii*
8	Kaohsiung	Left third finger	Paresthesia, cyanosis change, and numbness	Amoxicillin/clavulanic acid	Fasciotomy	0.5 day	No	0.9 days	No growth
9	Kaohsiung	Right first finger	Progressive swelling, and hemorrhagic bullae	Amoxicillin/clavulanic acid	Debridement and fasciotomy	1 day	Yes	11.6 days	*E. cloacae*
10	Kaohsiung	Left third finger	Ecchymosis and several small bullae	Amoxicillin/clavulanic acid	Fasciotomy	1 day	No	11.0 days	No growth
11	Kaohsiung	Right first finger	Progressive swelling and ecchymosis	Ampicillin/sulbactam	Debridement and fasciotomy	1 day	No	11.2 days	No growth
12	Kaohsiung	Right first finger	Paresthesia, cyanosis change and numbness, progressive swelling, and necrosis	Amoxicillin/clavulanic acid	Debridement, fasciotomy, and flap	0.5 day	Yes	8.6 days	No growth
13	Kaohsiung	Right first finger	Rapid progressive swelling, local erythema, and tense skin	Ampicillin/sulbactam	Debridement, fasciotomy, and flap	0.5 day	No	9.8 days	No growth
14	Kaohsiung	Left hand	Rapid progressive swelling	No antibiotic	Debridement and fasciotomy	0.16 day	No	10.2 days	Not performed

C. jeikeium = *Corynebacterium jeikeium*; *E. cloacae* = *Enterobacter cloacae* complex; *E. faecalis* = *Enterococcus faecalis*; HLOS = hospital length of stay; *M. morganii* = *Morganella morganii*; *S. putrefaciens* = *Shewanella putrefaciens*.

TABLE 5
Antibiotic susceptibility of *E. cloacae* complex, *E. faecalis*, and *M. morganii*

	E. cloacae		*E. faecalis*		*M. morganii*
Antibiotics	Normal oral flora of TS ($N = 7$)	Wound culture after TS bites ($N = 2$)	Normal oral flora of TS ($N = 11$)	Wound culture after TS bites ($N = 2$)	Wound culture after TS bites ($N = 2$)
Ampicillin	–	–	11S	2S	–
Amikacin	7S	2S	–	–	2S
Ceftazidime	6S	1S	–	–	2S
Ciprofloxacin	6S	2S	–	–	2S
Cefoperazone/sulbactam	7S	1S	–	–	–
Ceftriaxone	6S	1S	–	–	2S
Cefuroxime	6S	–	–	–	2S
Cefazolin	–	–	–	–	–
Ertapenem	7S	1S	–	–	2S
Gentamicin	7S	1S	–	–	2S
Gentamicin (120 μg)	–	–	11S	2S	–
Levofloxacin	7S	2S	–	–	2S
Penicillin	–	–	11S	2S	–
Ampicillin/sulbactam	3S	1S	–	–	2S
Sulfamethoxazole/trimethoprim	–	–	–	–	2S
Teicoplanin	–	–	11S	2S	–
Piperacillin/tazobactam	7S	1S	–	–	2S
Vancomycin	–	–	11S	2S	–

E. cloacae = *Enterobacter cloacae* complex; *E. faecalis* = *Enterococcus faecalis*; *M. morganii* = *Morganella morganii*; S = susceptible; TS = *Trimeresurus stejnegeri*. The data on the oral flora of TS in Taiwan were obtained from a previous study.[36]

wound infection. All of the above factors account the discrepancies between north and south Taiwan.

Deciding whether to undergo surgery is indeed a dilemma, with some surgical criteria jointly determined by clinical physicians and surgeons. Previous studies have reported that intracompartmental syndrome involves severely envenomed muscles that are not viable and, therefore, will not benefit from fasciotomy.[46,47] However, the criteria for fasciotomy in snakebite, as outlined in the WHO guidelines,[34] include 1) clinical evidence of an intracompartmental syndrome and 2) intracompartmental pressure $>$ 40 mm Hg (in adults). In our study, all patients who underwent surgery exhibited normal coagulation function, and there were no postoperative mortalities.

More than 60 different pathogens were identified in a previous study,[39] five of which were cultured in our study. Snakebite wound infections are often polymicrobial, with *E. cloacae* complex, *E. faecalis*, and *M. morganii* being the most commonly isolated pathogens, which is similar to the bacterial flora of the oral cavity of venomous snakes.[36] It is more certain that the snake oral cavity is colonized by bacteria that can be transmitted to patients through skin injury caused by biting. There is no consensus on the use of antibiotics as initial therapy. Early studies recommended prescribing empiric antibiotics for snakebite wounds.[48,49] However, subsequent studies reported that the use of prophylactic antibiotics is not effective in preventing local infections.[50,51] Antibiotic administration should be considered only in snakebitten patients with severe local signs of envenomation. In recent studies, the majority of isolated bacteria showed resistance to amoxicillin-clavulanate (60–82.9%) and ampicillin (69%), which was most commonly used for superficial skin wounds.[50,52,53] In our study, Enterobacteriaceae after snakebite-related infections were resistant to ampicillin-sulbactam (50%), and all were resistant to cefazolin and cefuroxime. However, bacteria were susceptible to ciprofloxacin and levofloxacin in all cases. The prescribed antibiotics should cover the oral microbiota commonly found in *T. stejnegeri* for patients with severe snakebite-induced wound infections. This will result in a shift in the clinical management of snakebite-related wound infections.

Study limitations. Our study has several limitations. First, this was a retrospective study, and data were systematically collected from the Chang Gung Research Database, which is based on original electronic medical records. Not all detailed clinical manifestations necessary for the precise assessment of poison severity scale or envenoming grade could be obtained. Second, although this study was conducted at the largest hospital in Taiwan, the number of included patients was insufficient. Third, referral bias may have existed because we included patients from medical centers only. Finally, whether a wound is infected depends on the subjective judgment of the physician based on the clinical condition at the time, without any consistent criteria. Despite these limitations, this is the first study to investigate the risk factors for wound infections by *T. stejnegeri*.

CONCLUSION

The wound infection rate was 25.6% among patients bitten by *T. stejnegeri*. The factor associated with wound infection is delayed initiation of antivenom administration. Early initiation of antivenom treatment (within 6 hours) can reduce the risk of wound infection. Empiric antibiotics such as amoxicillin-clavulanate and first- or second-generation cephalosporins are not recommended for snakebite wound infections because of the high resistance of bacteria to these antibiotics. Prophylactic antibiotics are not routinely recommended. However, when an infection is highly suspected, we propose that broad-spectrum antibiotics be considered for treatment. Third-generation cephalosporins, quinolones, and piperacillin/tazobactam are recommended because snakebite wound infections are often polymicrobial.

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