Acute Kidney Injury and Rhabdomyolysis after *Protobothrops flavoviridis* Bite: A Retrospective Survey of 86 Patients in a Tertiary Care Center

Hiroaki Nishimura,* Hideki Enokida, Shuichirou Kawahira, Ichiro Kagara, Hiroshi Hayami, and Masayuki Nakagawa

Division of Blood Purification, Kagoshima Prefectural Ohshima Hospital, Kagoshima, Japan; Department of Urology,
Graduate School of Medical and Dental Sciences, Kagoshima University, Kagoshima, Japan;
Blood Purification Center, Kagoshima University Hospital, Kagoshima, Japan

Abstract. Acute kidney injury (AKI) is the main cause of death for victims of hematoxic snakebites. A few studies have described improvement in AKI rates in snakebite cases, but the reasons for the improvement have not been investigated. Eighty-six patients with *Protobothrops flavoviridis* bites admitted to a single center from January 2003 through March 2014 were included in the study. Clinical variables, including age, sex, blood pressure (BP), and serum creatinine (S-Cr), on admission were compared between patients with and without AKI. One patient died of disseminated intravascular coagulation following AKI (mortality rate 1.1%). Six patients developed AKI with rhabdomyolysis. Systolic BP, S-Cr, serum creatine kinase, white blood cell count, and platelet count differed significantly between the AKI and non-AKI groups ($P = 0.01$). Three of the six patients were physically challenged to a degree that made it difficult for them to move or communicate, and these difficulties likely exacerbated the severity of snakebite complications. Our study demonstrated that the risk of snakebite-induced AKI for physically challenged patients was high. To further reduce mortality due to snakebite-induced AKI, we need to make it possible for physically challenged patients to receive first aid sooner.

INTRODUCTION

Over 3,000 species of snakes are known worldwide, of which around 600 are poisonous species belonging to the families Viperidae, Elapidae, Hydrophiidae and Colubridae, and Atractaspididae. Poisonous snakebites are an important health hazard because of their incidence, morbidity, and mortality.¹ Even though antivenom serum is effective, the World Health Organization (WHO) added snakebites to the list of neglected tropical diseases in 2009 because it estimates that every year there are approximately 125,000 deaths due to 2,500,000 poisonous snakebites.²

Because the fatality rate for snakebite cases tends to be high in rural areas of developing countries, snakebites in those countries have usually been investigated by comparing between groups of victims with fatal and nonfatal outcomes.^{3,4} Several studies have identified fatal complications of hemotoxic snakebites, and acute kidney injury (AKI) has been identified as the most important cause of death among patients surviving the early effects of envenomation by the *Crotalus* and *Bothrops* genera of the Viperidae family.⁵ Other characteristics at admission have also been found to be risk factors for fatal outcome, and a few studies have described the chronological improvement for fatality rates and complication rates in snakebite.⁶ The reasons for this improvement, though, have not been investigated. Moreover, it is hard to see what should be done next to reduce the fatality rates of snakebite victims.

Among the indigenous venomous snakes of medical importance in Japan, *Protobothrops flavoviridis*, belonging to the Viperidae family, is a major poisonous snake in terms of its toxicity and ferocity and the damage its bite causes. This venomous snake causes most unfavorable and severe clinical events, as evidenced by the occurrence of local and/or systemic complications. The envenomations by the Viperidae family

generally lead to the same spectrum of complications.⁷ These complications are prone to cause AKI, which is the main organ damage observed after Viperidae bites. There were epidemiological studies about snakebites on Amami Ohshima islands,^{8–10} but there have been no large studies of the temporal development of AKI caused by *P. flavoviridis* venom.

We conducted a retrospective analysis of patients admitted to a tertiary medical center on Amami Ohshima Island after envenomation by *P. flavoviridis*. This verification clarified the occurrences of these snakebites on Amami Ohshima and their mortality and fatal general symptoms, especially AKI and rhabdomyolysis. The objectives of this study were to determine the risk factors associated with a fatal outcome and to assess strategies to reduce the risk of fatal outcome.

MATERIALS AND METHODS

Setting and study design. This retrospective study on the victims of *P. flavoviridis* was conducted at the Kagoshima Prefectural Ohshima Hospital from January 2003 to March 2014. Ethical approval was obtained from the Ethical Review Committee of the Kagoshima Prefectural Ohshima Hospital. This hospital is a tertiary care center and one of the main referral centers for snakebite cases in the region. Located in Naze, Amami City—the central city of Amami Ohshima Island—it serves all the island's residents and admits those with snakebites. Some of the snakebite victims included in this study were admitted to this hospital after receiving first aid treatment at a rural clinic. Antivenom was administered depending on the symptoms, and tetanus toxoid and human anti-tetanus immunoglobulin were used when required. After the admission, all patients were hydrated with an alkalinizing solution according to their clinical picture. The condition of each of the snakebite patients admitted to the hospital was followed up from the time of admission to the end of their hospital stay.

Amami Ohshima Island. Amami Ohshima Island, in Japan's Kagoshima prefecture, is the largest of the Amami Ohshima islands. Lying at latitude 27°0'53''–28°32'30''N and longitude 128°23'50''–130°2'16''E, it is surrounded on the southwest by

*Address correspondence to Hiroaki Nishimura, Division of Blood Purification, Kagoshima Prefectural Ohshima Hospital, 18-1 Nazemanatsu-cho, Amami City, Kagoshima 894-0015, Japan. E-mail: nishimura.hiroaki@gmail.com

the East China Sea and on the northeast by the Pacific Ocean. Since the climate of the island is subtropical maritime, the island is frequently hit by typhoons and heavy rain. As a result, the annual mean air temperature is over 20°C (70°F) and the annual mean precipitation is over 2,800 mm (Japanese annual mean precipitation is 1,700 mm.). Over 85% of the island is mountainous and covered with subtropical broad-leaved evergreen forest. The area of the island is 712.52 km² and the population is estimated at over 68,000.¹¹

Venomous snakes on Amami Ohshima islands. Of the four species of venomous snakes indigenous to Amami Ohshima islands (*P. flavoviridis*, *Ovophis okinavensis*, *Amphiesma pryeri*, and *Sinomicrurus japonicus*), *P. flavoviridis*, of the Viperidae family and Crotalinae subfamily, is responsible for most cases of envenomation.¹² The venom of *P. flavoviridis* causes local damage and sometimes life-threatening systemic damage. This snake's venom is hemorrhagic, necrotic, and hemolytic. The identification of snakes was documented by emergency physicians on the basis of the descriptions of the biting snake given by the patients and relatives as well as the envenomation symptoms. *Protobothrops flavoviridis* is easily distinguished because of the local symptoms of its bite, its distinctive color pattern, and its distinctive total length.

Clinical parameters and laboratory evaluation. The bite site, the time between the snakebite and administration of antivenom (bite-to-needle time), and mortality were noted. Age, gender, body mass index, history of comorbid illness, use of concomitant drugs, hospitalization, bleeding manifestations, regional lymphadenopathy, urinary abnormality, and general condition were recorded. Systolic and diastolic blood pressures (BPs) were evaluated daily.

A blood sample was collected at admission and daily until 72 hours after the snakebite. These samples were collected to measure sodium, potassium, serum creatinine (S-Cre), aspartate aminotransferase (AST), alanine aminotransferase (ALT), serum creatine kinase (CK), lactate dehydrogenase (LDH), prothrombin (PT), activated partial thromboplastin time, fibrinogen, hematocrit, hemoglobin, white blood cells (WBCs), and platelets (Plt.). When the patients showed systemic complications, blood specimens were collected every day until discharge or the symptoms were dismissed.

Classification of systemic complication. In the literature, the clinical symptom of *P. flavoviridis* envenoming range from local complications (pain, swelling, erythema, etc.) to systemic complications (AKI, rhabdomyolysis, spontaneous bleeding, etc.). In this study, the clinical symptoms and complications of snake envenoming were classified using WHO guidelines for the clinical management of snakebites in the southeast Asian region.¹³

We diagnosed AKI according to the following criterion: S-Cre increased to > 1.5 times a baseline known or presumed to have occurred within the prior 7 days.¹⁴ The clinical diagnosis of rhabdomyolysis was then established when CK increased five or more times normal levels, with a suggestive clinical picture and without heart and cerebral injury.^{5,15}

Statistical analysis. Patients were analyzed as a group and were later allocated into two groups according to the presence or absence of systemic complications. On-admission data differences between the two groups were compared using χ^2 test or the Mann-Whitney test wherever required. All tests were two sided, with a *P* value of ≤ 0.01 considered statistically significant.

RESULTS

Analyzed sample. During the study period, a total of 89 cases of *P. flavoviridis* bite were identified in medical records. First, we excluded the study patients who had clinical and/or laboratory evidence of chronic kidney disease. Chronic kidney disease was defined as the baseline S-Cre value more than 2 mg/dL and/or past history of active renal disease. Second, basically the condition of each *P. flavoviridis* bite patient admitted to our hospital was followed up from the time of admission to the end of their hospital stay. But some patients refused to stay in hospital after receiving medical aid at the outside emergency department. These exclusion criteria resulted in three patients not being included in the study. The included cases were further confirmed on the basis of local clinical symptoms. So, a total of 86 patients were eligible for final analysis.

The *P. flavoviridis* bite victims were predominantly male (*N* = 71), and the male to female ratio was 4.7:1. The mean age of the male victims was 54.6 years (range = 11–78 years) and that of the female victims was 68.4 years (range = 25–86 years). The bites occurred during while farming activities (*N* = 28), householding activities (*N* = 3), while walking (*N* = 7), hunting (*N* = 28), and doing other work (*N* = 20). Because the health center of the Amami islands purchases *P. flavoviridis* brought by inhabitants (for research and to reduce the number of these snakes), some inhabitants hunt these venomous snakes.¹² The bite sites ranged from the head to the legs, and upper limbs were involved four times more often than under limbs. The chief presenting complaint was local swelling and pain at the site of bite in all patients.

All patients reached the emergency room within 12 hours of the bite, and specific treatment was started immediately. Some were brought by an ambulance, private automobile, or motorcycle; others simply walked. Average time from snakebite to specific antivenom administration was 1 hour (range = 0.2–12 hours). Specific anti-snake venom treatment was given in 84 cases: 82 patients got one vial and two patients got two vials of antivenom. About 15% received antivenin at a village-based primary health center before they were referred to our hospital (Table 1).

Occurrence of systemic complications. In our study, the life-threatening systemic complications were defined as AKI, rhabdomyolysis, and disseminated intravascular coagulation (DIC). Six patients developed AKI, seven rhabdomyolysis, and one DIC.

DIC was the cause of death in that patient, who also suffered AKI and rhabdomyolysis, despite continuous hemodiafiltration being undertaken. The mortality rate in our study was 1.1%.

Comparison of the AKI and non-AKI groups. Of the 86 patients studied, six patients required developed AKI. The baseline demographic and clinical characteristics of the 86 patients grouped according to their outcome status are listed in Table 2. All patients who developed AKI despite antivenom therapy were hospitalized within 72 hours after the snakebite. Only one patient required continuous hemodiafiltration.

AKI patients tended to be older than non-AKI patients (74 [52–86] years versus 55 [11–83] years), but this difference was also not statistically significant at the 1% level (*P* = 0.0102). The non-AKI group included more males. The on-admission systolic BP of the AKI group (105 [60–120] mmHg) was significantly (*P* = 0.0011) lower than that of the non-AKI

TABLE 1

Demographic and clinical characteristics of 86 patients on Amami Ohshima Island with *Protobothrops flavoviridis* bites

Characteristics	N = 86
Gender	
Male	71
Female	15
Age, mean $\pm$ SD	
Male	54.6 $\pm$ 13.5
Female	68.4 $\pm$ 14.8
Type of activity at the time of bite	
Farming activities	28
Householding activities	3
Walking	7
Hunting	28
Doing other work	20
Bite sites	
Head	2
Upper limbs	68
Under limbs	16
Amount of antivenom in units	
0	2
1	82
2	2
Life-threatening complications	
Acute renal impairment (AKI)	6
Rhabdomyolysis	7
Disseminate intravascular coagulation	1
Duration of hospitalization (days), mean $\pm$ SD	9.6 $\pm$ 11.6

AKI = acute kidney injury; SD = standard deviation.

group (148 [82–233] mmHg). The on-admission diastolic BP of the AKI group (85 [53–122] mmHg) tended to be higher than that of the non-AKI group (72 [40–84] mmHg), but the difference was not significant ($P = 0.0446$). Systolic BP, Cre, CK, WBCs count, and Plt. count on admission differed significantly between the AKI group and the non-AKI group, but the bite-to-needle time did not. There was no between-group difference in the amount of antivenom administered either in the first aid treatment or after admission. Both groups received similar hydration after admission.

All of the patients in the non-AKI group, with or without first aid, visited our center immediately after the snakebite, whereas three of the six patients in the AKI group were transported to our center after they had been left untreated for a few hours after the snakebite. Each of those patients had a previous history of cerebral infarction, polio, or dementia. The aftereffects of these diseases made harder

for patients to reach or ask for medical aid. Therefore, these difficulties exacerbated their snakebites envenomation. The number of physically challenged patients differed significantly ($P = 0.0001$) between the AKI group and the non-AKI group.

Renal function. The S-Cre values of all six patients in the AKI group increased after admission. Despite the initial fluid infusion, three of those patients decreased urinary volume and required the use of diuretics. The other three recovered renal function after the fluid infusion. Although as mentioned above, one of the AKI patients died, the S-Cre values of the other five had recovered to the baseline level or lower by the time the patients were discharged (Table 3).

Laboratory evaluation of rhabdomyolysis. After admission, seven patients had hypercreatinine kinasemia data indicating rhabdomyolysis. Six of them had systemic features accompanying rhabdomyolysis, AKI, and thrombocytopenia, but the other demonstrated only hypercreatinine kinasemia. This patient had snake venom-induced local muscle and tissue impairment. CK values in the AKI group were significantly higher than those in the non-AKI group (Table 4). The highest values reached levels 73 times higher than normal. AST, ALT, and LDH at admission did not differ significantly between the AKI and non-AKI groups, but the peak levels of these parameters during hospitalization did (Table 5). However, myoglobinuria was not measured routinely.

DISCUSSION

To our knowledge, this is the first retrospective study of severe general clinical events after *P. flavoviridis* bites in the last decade. This study indicated the issues that must be dealt with if the mortality of bite victims is to be improved. Although most snakebite victims in Japan visit a hospital's emergency room immediately and receive prompt first aid measures, the bites of poisonous snakes can be fatal because of the virulence of the venom. The lethal dose (LD₅₀: μ g/mouse) is 177–191 for *P. flavoviridis* venom, 22–35 for *Crotalus durissus* venom, and 128–144 for *Bothrops nasutus* venom.¹⁶

Various recent epidemiological studies of *P. flavoviridis* bites have reported mortality rates, but there are few that demonstrate the change in the mortality rate over 100 years. Examining the literature, we found that the recent mortality rate has reached a level much lower than that in the early

TABLE 2
Comparison between two groups for demographic and clinical characteristics of patients at admission

	AKI group (N = 6)	Non-AKI group (N = 80)	P value
Demographics			
Age (years)	74.16 $\pm$ 13.51	55.78 $\pm$ 16.80	0.0102
Males (%)	50	85	0.0629
Physically challenged patients (head count)	3	0	0.0001
Bite-to-needle time (hours)	3.50 $\pm$ 4.32	0.91 $\pm$ 0.57	0.0187
BMI (kg/m ²)	22.96 $\pm$ 2.18	24.33 $\pm$ 4.16	0.5044
Systolic BP (mmHg)	105.00 $\pm$ 23.21	148.28 $\pm$ 26.90	0.0010
Diastolic BP (mmHg)	85.23 $\pm$ 15.56	72.33 $\pm$ 16.31	0.0446
Heart rate (bpm)	86.66 $\pm$ 12.61	83.37 $\pm$ 15.80	0.3697
Laboratory characteristics			
S-Cre (mg/dL)	1.43 $\pm$ 0.45	0.77 $\pm$ 0.13	< 0.001
CK (IU/L)	1,224.83 $\pm$ 1,221.07	210.28 $\pm$ 305.93	< 0.001
WBCs (/ μ L)	14,293.33 $\pm$ 3,048.95	7,875.51 $\pm$ 3,177.29	< 0.001
Plt. ($\times 10^4/\mu$ L)	9.08 $\pm$ 6.01	20.09 $\pm$ 6.13	0.0014

AKI = acute kidney injury; BMI = body mass index; BP = blood pressure; CK = creatine kinase; Plt. = platelets; S-Cre = serum creatinine; WBCs = white blood cells.

TABLE 3
S-Cre (mg/dL) comparison between AKI and non-AKI groups

	AKI group (N = 6)	Non-AKI group (N = 80)	P value
Baseline S-Cre	0.73 ± 0.12	0.85 ± 0.08	0.0286
S-Cre at admission	1.43 ± 0.12	0.77 ± 0.13	< 0.001
Peak of S-Cre	2.21 ± 0.72	0.08 ± 0.12	< 0.001
Discharge S-Cre	0.82 ± 0.04*	0.74 ± 0.12	0.1642

AKI = acute kidney injury; S-Cre = serum creatinine.
*N = 5 (one AKI patient died before being discharged).

20th century. Before 1904, the fatality rate for *P. flavoviridis* bite cases was approximately 10%.⁸ During the past six decades, however (since the 1950s), it has been decreasing as a result of improvements of the antivenom serum, the availability of that serum in villages, advances in the means of transportation, and the progression of anti-collapse treatment. Since 2005, there have been 15–33 cases/year of *P. flavoviridis* bite in Kagoshima (Web site of Kagoshima prefecture, in Japanese),¹² and in our epidemiological study, the mortality rate was only 1.1%. Although there has been little data on the bite symptoms, this study shows that *P. flavoviridis* in Japan caused severe clinical events evidenced by the systemic complications of AKI, rhabdomyolysis, and DIC. The cause of death was DIC in one case, although AKI had a major impact on the clinical course. It was the most significant systemic complication and may be the one with the strongest influence on the prognosis.

The venom of *P. flavoviridis* contains high concentrations of biologically active proteins, mainly phospholipase A₂ and protease.¹⁷ These proteins, and intrinsic toxins released from the local necrotic tissue, would promote bleeding, the pooling of blood and fluids, and circulatory collapse. These clinical abnormalities are known to favor the development of AKI. Depending on the species of snake, the incidence of AKI caused by the snake venom varies from 5% to 32%.^{5,18–20} The reason for the variety in the incidence of AKI is that the development of AKI after snakebites is affected to some degree by various independent factors. Some of those identified in experimental studies of the mechanisms involved in AKI development after *P. flavoviridis* bites are direct nephrotoxicity.²¹ Moreover, the social contributing factors—poor access to adequately equipped and staffed medical centers, the high cost of treatment, and inadequate use of antivenom—are also of major concern as AKI risk factors.^{6,22}

Year-by-year improvement of those social factors may have also improved the prognosis of *P. flavoviridis* bite victims.^{9,12} The use of antivenom serum was especially effective in reducing the fatality rate.^{5,23} On the other hand, in our study, the bite-to-needle time for the administration of antivenom serum did not differ significantly between patients who developed AKI and patients who did not. This is particularly notable because previous studies of other snakebites had found that

TABLE 4
Serum CK (IU/L) comparison between AKI and non-AKI groups

	AKI group (N = 6)	Non-AKI group (N = 80)	P value
CK at admission	1,224.83 ± 1,221.07	210.84 ± 305.93	< 0.001
Peak of CK	9,265.00 ± 8,131.45	684.08 ± 1,447.76	0.0005
Discharge CK	38.20 ± 12.89*	95.34 ± 80.19	0.0240

AKI = acute kidney injury; CK = creatine kinase.
*N = 5 (one AKI patient died before being discharged).

TABLE 5
AST (IU/L), ALT (IU/L), and LDH (IU/L) comparison between AKI and non-AKI groups

	AKI group (N = 6)	Non-AKI group (N = 80)	P value
AST at admission	40.83 ± 18.56	31.81 ± 24.18	0.0247
Peak of AST	2,121.83 ± 4,014.24	51.14 ± 69.19	0.0001
Discharge AST	19.00 ± 4.52*	31.45 ± 30.87	0.1807
ALT at admission	16.00 ± 3.28	28.61 ± 24.40	0.0879
Peak of ALT	832.16 ± 1,485.05	38.25 ± 38.51	0.0003
Discharge ALT	57.40 ± 61.62*	28.90 ± 24.38	0.5628
LDH at admission	273.83 ± 75.10	252.32 ± 95.50	0.3775
Peak of LDH	1,858.00 ± 2,705.16	260.76 ± 108.24	0.0005
Discharge LDH	321.20 ± 301.78*	210.20 ± 80.24	0.5466

AKI = acute kidney injury; ALT = alanine aminotransferase; AST = aspartate aminotransferase; LDH = lactate dehydrogenase.

*N = 5 (one AKI patient died before being discharged).

delayed antivenom administration increased the risk of AKI. This discrepancy is probably related to the year-by-year reduction of the time before starting treatment. Our bite-to-needle time for antivenom serum administration is shorter than those reported previously.^{3,23,24} Shortening the bite-to-needle time for antivenom serum administration and improving the care setting could reduce the mortality rate of snakebites to 1.1%. Furthermore, pit viper envenomation often results in a consumptive coagulopathy manifested by a decreased Plt. count, a prolonged PT time, or hypofibrinogenemia.¹ The comparison of Plt. count at the admission in our study revealed that AKI was associated with more severe thrombocytopenia. As an intravascular bleeding tendency because of DIC was reported to be the pathogenetic factor in the development of AKI,²³ thrombocytopenia probably has a close connection with the AKI induced by *P. flavoviridis* envenomation. It was, though, possible that exacerbation had been prevented by antivenom, since in all cases except one thrombocytopenia had been improved after the antivenom administration. Earlier antivenom treatment could reduce the degree of thrombocytopenia and the likelihood of AKI. The extreme importance of an early antivenom administration is evident, and our data demonstrate better than previous data that earlier treatment would reduce the mortality rate.

Rhabdomyolysis is another clinical complication known to be one of the causes of AKI. Snake phospholipase A₂ can cause rhabdomyolysis and hemolysis, for which CK is considered the most sensitive marker.^{5,15} In addition, AST, ALT, and LDH are adopted as other laboratory parameters. These parameters reached peak values during the hospitalization, which might have demonstrated the occurrence of hemolysis in addition to the exacerbation of rhabdomyolysis. However, it is hard to make a precise diagnosis about above condition because free hemoglobin, haptoglobin, and urinary myoglobin were not measured in our study. Solving these diagnosis problems will require further studies including these laboratory parameters.

As a broad array of causes is related to the development of AKI, it is difficult to identify the cause of AKI after a snakebite. If it were identified, though, a tailor-made therapy could be undertaken. Also, regarding the rhabdomyolysis induced by the bite of a venomous snake, it is possible to detect its cause and choose an effective treatment accordingly. The AKI induced by rhabdomyolysis after a snakebite can be prevented by vigorous hydration because the following intense urinary flow reduces the exposure of the renal

tubular epithelium to myoglobin. Because the consequences of rhabdomyolysis are so severe, it should be prevented more aggressively.

In our study, the patients with AKI had a higher WBCs counts at admission than did the patients without AKI. Elevation of WBCs counts is usually observed in cases with infection and/or tissue damage. Athappan and others reported that the presence of cellulitis was a significant independent factor related to AKI because the swelling of the bitten part of a limb can spread to involve the whole limb, and bleeding and loss of plasma into the bitten extremity can produce circulatory collapse.²³ Consequently, the elevation of WBCs counts is presumed to be a prodrome of the local severe inflammation resulting in AKI. From the perspective of preventing AKI as well, the treatments to ameliorate local tissue damage are critical. Other than antibiotic treatment and surgical treatment of local manifestations of pit viper bites, one of primary options in Japan is a biscoclaurine amphipathic alkaloid. Hifumi and others reported that the biscoclaurine amphipathic alkaloid, cepharanthine, lessens the inflammation and pain caused by *Gloydius blomhoffii* bites.²⁵ But large-scale prospective studies would be needed to find out whether it is also effective for *P. flavoviridis* bites.

The hypotensive effects of *P. flavoviridis* venom had been reported in experimental animal studies.²⁶ The hypotension exerted an influence on AKI development after *P. flavoviridis* bites. In the pathogenesis of AKI after snakebites, impaired renal hemodynamics is taken as one of the causes. Early circulation support treatment of hypotension could prevent the deterioration of renal function.⁵ Our data suggest the importance of initial therapy to prevent AKI.

Kalantri and others reported that the S-Cre concentration on admission was a strong predictor of mortality in snakebite cases and that AKI was strongly associated with the prognosis in these cases. In our study, the admission S-Cre concentration differed significantly between the AKI group and the non-AKI group, so elevation of S-Cre at admission was a prognostic factor for *P. flavoviridis* envenomation-induced AKI. This suggests that snakebite nephrotoxicity develops within the first few hours. It is difficult, however, to determine from our study the degree of S-Cre elevation predicting AKI occurrence. It is therefore advisable to be hospitalized for observation after a *P. flavoviridis* bite.

Among the limitations of our study are the sample size and the retrospective design. Our sample was not large because we did not receive data from all the clinical centers on Amami Ohshima Island. As mentioned above, there have been 15–33 cases/year of *P. flavoviridis* bite on Amami Ohshima Island. Therefore, our study surveyed approximately one-third of the annual number of *P. flavoviridis* bite cases on the island. The design issue was addressed by strict classification of clinical outcome, although the retrospective study did not always yield reliable clinical data.

In conclusion, our study demonstrated that AKI was the most life-threatening systemic complication of *P. flavoviridis* envenomation. The mortality of this envenomation has been decreased over the past 100 years from 10% to 1.1%, but further efforts are required if it is to be reduced even more. AKI occurred more frequently in snakebite-envenomation patients who on admission had lower systolic BPs and higher S-Cr and CK levels and WBCs and Plt. counts. Our speculation could indicate countermeasures against these risk pre-

dictors. In addition, examination of the past medical history of snakebite-induced AKI patients revealed that being physically challenged had much effect on the occurrence of *P. flavoviridis*-envenomation AKI. To further reduce the occurrence of snakebite-induced AKI, it will be necessary to construct an emergency hospital service system in which these kinds of patients can receive treatment sooner.

Received July 27, 2015. Accepted for publication November 3, 2015.

Published online December 7, 2015.

Acknowledgments: We thank Dr. Shoji Natsugoe for his review of this manuscript and the staff at Kagoshima Prefectural Ohshima Hospital for their support and cooperation during the study.

Authors' addresses: Hiroaki Nishimura, Shuichirou Kawahira, and Ichiro Kagara, Division of Blood Purification, Kagoshima Prefectural Ohshima Hospital, Kagoshima, Japan, E-mails: nishimura.hiroaki@gmail.com, kawashu999@yahoo.co.jp, and himawarisaita5215@yahoo.co.jp. Hideki Enokida and Masayuki Nakagawa, Department of Urology, Graduate School of Medical and Dental Sciences, Kagoshima University, Kagoshima, Japan, E-mails: enokida@m.kufm.kagoshima-u.ac.jp and nakagawa@m.kufm.kagoshima-u.ac.jp. Hiroshi Hayami, Blood Purification Center, Kagoshima University Hospital, Kagoshima, Japan, E-mail: bass@m.kufm.kagoshima-u.ac.jp.

REFERENCES

1. Gold BS, Dart RC, Barish RA, 2002. Bites of venomous snakes. *N Engl J Med* 347: 347–356.
2. Chippaux JP, 1998. Snake-bites: appraisal of the global situation. *Bull World Health Organ* 76: 515–524.
3. Monterio FNP, Kanchan T, Bhagavath P, Kumar GP, Menezes RG, Yoganarasimha K, 2012. Clinico-epidemiological features of viper bite envenomation: a study from Manipal, south India. *Singapore Med J* 53: 203–207.
4. Punde DP, 2005. Management of snake-bite in rural Maharashtra: a 10-year experience. *Natl Med J India* 18: 71–75.
5. Pinho FM, Zanetta DM, Burdman EA, 2005. Acute renal failure after *Crotalus durissus* snakebite: a prospective survey on 100 patients. *Kidney Int* 67: 659–667.
6. Sharma SK, Chappuis F, Jha N, Bovier PA, Loutan L, Koirala S, 2004. Impact of snake bites and determinants of fatal outcomes in southeastern Nepal. *Am J Trop Med Hyg* 71: 234–238.
7. Kanjanabuch T, Sitprija V, 2008. Snakebite nephrotoxicity. *Semin Nephrol* 28: 363–372.
8. Wakisaka I, Miyashita M, Ando T, Takano A, 1978. An epidemiological study of habu-bites in the Amami Island. *Nippon Eiseigaku Zasshi* 33: 606–613.
9. Tomori T, 1987. An epidemiological study of the occurrence of habu snake bite on the Amami Islands, Japan. *J Epidemiol* 16: 451–461.
10. Yasunaga H, Horiguchi H, Kuwabara K, Hashimoto H, Matsuda S, 2001. Short report: venomous snake bites in Japan. *Am J Trop Med Hyg* 84: 135–136.
11. Nishimura H, Kagara I, Inokuchi S, Enokida H, Hayami H, Nakagawa M, 2014. Local dialysis disaster relief during two torrential downpours on Amami-Ohshima Island. *J Disaster Res* 9: 86–91.
12. Kagoshima University Repository, 2013. *The Islands of Kagoshima: Culture, Society, Industry and Nature* (Chapter 8). Available at: <http://hdl.handle.net/10232/17337>. Accessed March 15, 2013.
13. Warrell DA, 1999. WHO/SEARO guidelines for the clinical management of snake bites in the southeast Asian region. *Southeast Asian J Trop Med Public Health* 30: S1–S85.
14. Kellum JA, Lameire N, 2013. Diagnosis, evaluation, and management of acute kidney injury: a KDIGO summary (part 1). *Crit Care* 17: 204.
15. Vanholder R, Sever MS, Ereke E, Lameire N, 2000. Rhabdomyolysis. *J Am Soc Nephrol* 11: 1553–1561.
16. Theakston RD, Reid HA, 1983. Development of simple standard assay procedure for the characterization of snake venoms. *Bull World Health Organ* 61: 949–956.

17. Takeya H, Oda K, Miyata T, Omori-Satoh T, Iwanaga S, 1990. The complete amino acid sequence of the high molecular mass hemorrhagic protein HR1B isolated from the venom of *Trimeresurus flavoviridis*. *J Biol Chem* 265: 16068–16073.
18. Chugh KS, 1989. Snake bite induced acute renal failure in India. *Kidney Int* 35: 891–907.
19. Myint-Lwin, Warrell DA, Phillips RE, Tin-Nu-Swe, Tun-Pe, Maung-Maung-Lay, 1985. Bites by Russell's viper (*Vipera russelli siamensis*) in Burma: haemostatic, vascular, and renal disturbances and response to treatment. *Lancet* 2: 1259–1264.
20. Chugh KS, Pal Y, Chakravarty RN, Datta BN, Mehta R, Sakhuja V, Mandal AK, Sommers SC, 1984. Acute renal failure following poisonous snake bite. *Am J Kidney Dis* 4: 30–38.
21. Cattell V, Bradfield JW, 1977. Focal mesangial proliferative glomerulonephritis in the rat caused by habu snake venom. A morphologic study. *Am J Pathol* 87: 511–524.
22. Sharma SK, Bovier P, Jha N, Alirol E, Loutan L, Chappuis F, 2013. Effectiveness of rapid transport of victims and community health education on snake bite fatalities in rural Nepal. *Am J Trop Med Hyg* 89: 145–150.
23. Athappan G, Balaji M, Navaneethan U, Thirumalikulundusubramanian P, 2008. Acute renal failure in snake envenomation: a large prospective study. *Saudi J Kidney Dis Transpl* 19: 404–410.
24. Kalantri S, Singh A, Joshi R, Malamba S, Ezoua J, Morgan M, 2006. Clinical predictors of in-hospital mortality in patients with snake bite: a retrospective study from a rural hospital in central India. *Trop Med Int Health* 2: 22–30.
25. Hifumi T, Yamamoto A, Morokuma K, Okada I, Kiriu N, Ogasawara T, Hasegawa E, Kato H, Inoue J, Koido Y, Takahashi M, 2013. Clinical efficacy of antivenom and cepharanthine for the treatment of mamushi (*Gloydius blomhoffii*) bites in tertiary care center in Japan. *Jpn J Infect Dis* 66: 26–31.
26. Kinjo N, Noguchi K, Hirayama K, Sakanashi M, 1990. Characteristics of cardiovascular effects of the venom of habu (*Trimeresurus flavoviridis*) in rats. *Jpn J Pharmacol* 54: 151–161.