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Acute Kidney Injury Following Eastern Russell's Viper (*Daboia siamensis*) Snakebite in Myanmar

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Snakebite is a neglected tropical disease of global importance affecting at least 2.5 million people with more than 100,000 deaths annually.[1,2] Morbidity and mortality are high in countries such as Myanmar, where recent hospital data reported 15,000 to 20,000 cases per year with case-fatality ratio of 10.9%.[3] Experience elsewhere suggests that hospital-based data may underestimate the actual burden of snakebite by more than two-thirds.[4,5]

To assess outcomes of snakebite cases at Mandalay General Hospital, we established a clinical data collection system. This major hospital serves as a regional referral center for snakebite. In this region of Myanmar, Eastern Russell's Viper (ERV; *Daboia siamensis*) snakebite is of the utmost importance given the high incidence of acute kidney injury (AKI) following envenoming.[6,7]

The primary purpose of this clinical audit, which represents one arm of an Australian Department of Foreign Affairs and Trade–funded foreign aid project to improve the outcomes of snakebite patients in Myanmar,[8] is to provide accurate information to local health authorities to improve health care policies and resource allocation. In addition, we wanted to examine the clinical variables that affect the development of AKI following ERV envenoming. We report 12 months of observational data pertaining to ERV snakebites.

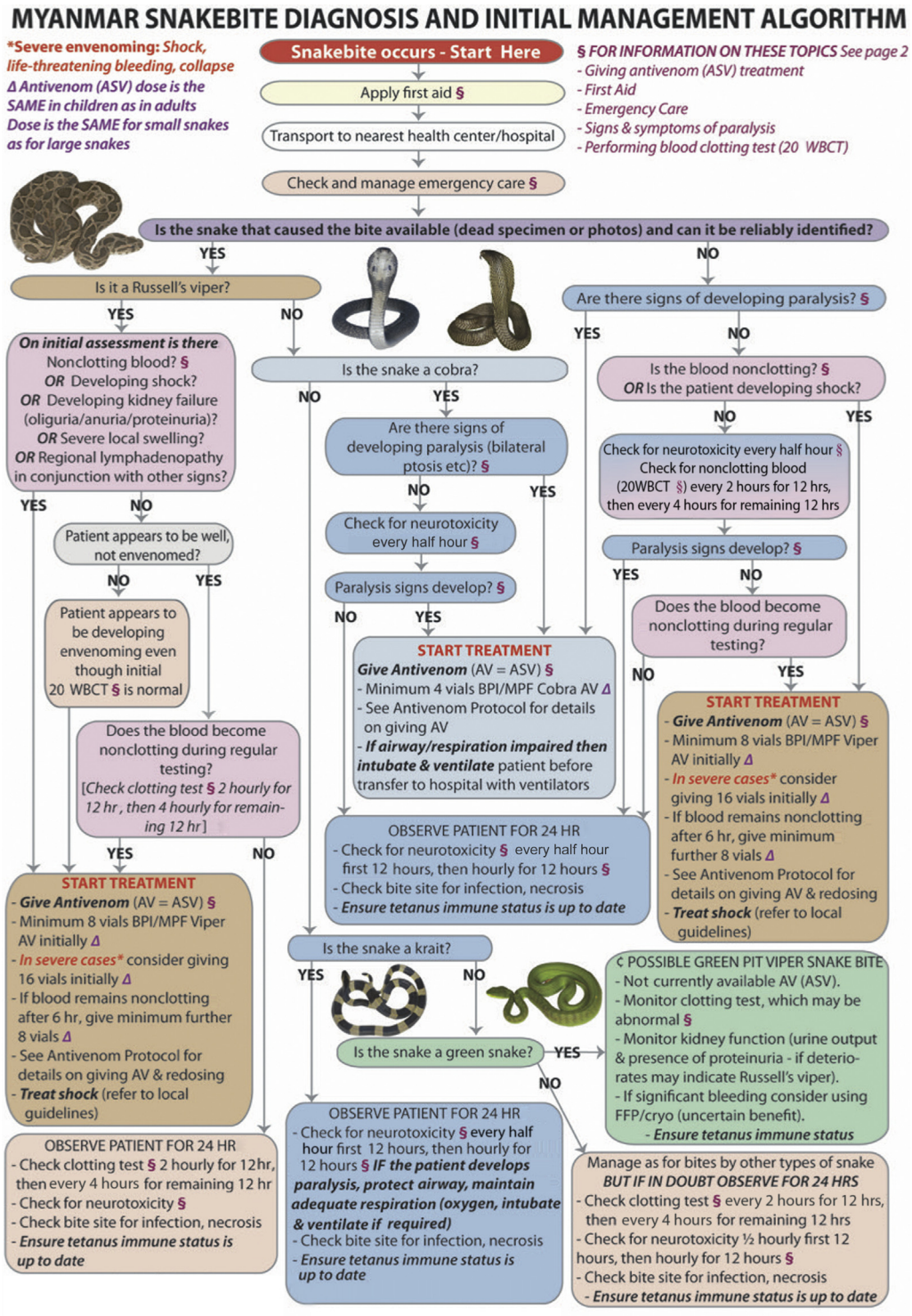

Figure 1. Myanmar national snakebite protocol. 20 WBCT, 20-minute whole blood clotting–test; ASV or AV, snakebite antivenom; BPI/MPF, Burma Pharmaceutical Industry/Myanmar Pharmaceutical Factory. Algorithm Copyright © 2018 Prof. Julian White. Snake photographs Copyright © 2018 Mark O'Shea. For page 2 of this management algorithm, please see White *et al.*[8]

RESULTS

A total of 965 patients presented to Mandalay General Hospital after snakebites during the 12-month period. Data for 17 patients were incomplete, leaving 948 for analysis. Bites were attributed to ERV in 686 cases (72.4%), cobra (*Naja kaouthia* and *Naja mandalayensis*) in 17 (1.8%), "green snake" (*Trimeresurus albolabris*) in 61 (6.4%), krait (*Bungarus* spp.) in 4 (0.4%), other snakes including nonvenomous species in 35 (3.7%), and unknown snakes in 145 (15.3%). In most cases, the dead snake was brought to the hospital and identified by medical staff. In the others, the diagnostic clinical

Table 1. Clinical features of 686 cases of Russell's Viper envenoming

Clinical features	Number (% of 686)	AKI group (% of 488)	No-AKI group (% of 198)
Acute kidney injury	488 (71)		
Coagulopathy	465 (67)	373 (76)	92 (47)
Thrombocytopenia	461 (67)	414 (85)	47 (24)
Capillary leak	240 (35)	216 (44)	24 (12)
Pulmonary edema	16	14	2
Periorbital edema	118	106	12
Conjunctival edema	91	82	9
Generalized edema	15	14	1
Shock	103 (15)	92 (19)	11 (6)
Bite site infection	74 (11)	51 (11)	23 (12)
Local necrosis	44 (6.4)	33 (7)	11 (6)
Gastrointestinal bleeding	38 (5.5)	33 (7)	5 (3)
Septicemia	29 (4.2)	26 (5)	3 (2)
Panhypopituitism	19 (2.7)	19 (4)	0
Ophthalmoplegia	2 (0.29)	2 (0.4)	0
None	59 (8.6)		

In this study, AKI was defined pragmatically as a composite endpoint of either requirement for dialysis *or*, in the absence of requirement for dialysis, a peak serum creatinine level of >120 μmol/l in men or >100 μmol/l in women *and* a pattern of rising serial creatinine consistent with AKI.

Table 2. Significant explanatory variables affecting AKI as determined by multivariate logistic regression

Explanatory variables	Group	AKI[a] (*surviving patients only in italics*) Sig. cf. Ref.Group	Odds ratio	Lower 95% CI	Upper 95% CI
Age group[b] (cf. 0–15 yr)	50–64 yr	$P < 0.05$ *$P < 0.05$*	2.8 *3.0*	1.1 *1.1*	7.2 *8.3*
Age group (cf. 0–15 yr)	>64 yr	$P < 0.01$ *$P < 0.01$*	5.5 *11.4*	1.6 *2.5*	19.6 *51.5*
Gender (cf. M)	F	$P < 0.01$ *$P < 0.02$*	1.8 *2.0*	1.2 *1.3*	2.7 *3.0*
Time bite to first AV[c] (cf. 0–1 h)	1–2 h	$P < 0.05$ *$P = 0.055$*	1.7 *1.8*	1.0 *1.0*	3.0 *3.2*
Time bite to first AV (cf. 0–1 h)	2–3 h	$P < 0.01$ *$P < 0.01$*	3.2 *2.8*	1.5 *1.3*	6.8 *6.2*
Time bite to first AV (cf. 0–1 h)	3–4 h	$P < 0.01$ *$P < 0.01$*	4.2 *4.2*	1.6 *1.5*	11.1 *11.6*
Time bite to first AV (cf. 0–1 h)	4–5 h	$P < 0.01$ *$P < 0.01$*	12.4 *12.5*	2.5 *2.3*	62.9 *67.3*
Time bite to first HCF[d] (cf. 0–1 h)	4–5 h	$P = 0.055$ *$P < 0.05$*	9.8 *10.0*	1.1 *1.1*	89.4 *91.5*
Time bite to first HCF (cf. 0–1 h)	>10 h	$P < 0.02$ *$P < 0.02$*	4.7 5.2	1.4 *1.4*	16.0 *19.7*

AKI, acute kidney injury; AV, antivenom; cf., compared with; CI, confidence interval; F, female; HCF, health care facility; M, male; Sig.cf.Ref.Group, significance compared with reference group.
Dependent variables:
[a]AKI, as defined as a composite endpoint of either requirement for dialysis *or*, in the absence of requirement for dialysis, a peak serum creatinine level of >120 μmol/l in men or >100 μmol/l in women *and* a pattern of rising serial creatinine consistent with AKI.
Categorical variables entered into the model, derived by coding continuous explanatory variables that did not exhibit a normal distribution:
[b]Age group, years: 0–15 (ref.); 16–19; 20–29; 30–49; 50–64; >64.
[c]Time from bite to first antivenom administration, hours: 0–1 (ref.); 1–2; 2–3; 3–4; 4–5; 5–6; 6–10; >10.
[d]Time from bite to arrival at first HCF.

syndrome combined with recognition by the patient of the familiar "mwe bwe" (ERV, *Daboia siamensis*) was accepted as sufficient identification. This report concentrates on ERV cases given that envenoming from this species alone accounts for 70% of all patients requiring acute nephrological care in Myanmar.[9]

Patients were typically male (64.9%) and had been bitten on the lower limbs during farm work. Median age was 34 (interquartile range [IQR] 24). Appropriate first aid (pressure pad and immobilization) was rarely applied. Tight tourniquets were applied commonly (77.8%); other interventions included incision (5.8%) and tattooing (8.9%). The first point of health care contact for most was either a rural health center or township hospital (82.8%), and traditional healers were consulted first in 13.9%. The median time from bite to arrival at a health care facility was 1.5 hours (IQR 2.19); the median time from bite to administration of the first dose of antivenom was 2 hours (IQR 3.5).

Almost all patients received antivenom (679, 98.9%); 295 cases (43%) received treatment considered compliant with national guidelines (initial dose of 8 vials of Burma Pharmaceutical Industry ERV monovalent antivenom, - $F[ab']_2$ fragments of equine hyperimmune plasma, for patients with significant features of ERV envenoming, see Figure 1). A common but noncompliant pattern in the remaining cases involved 1 to 2 vials given at a small health care facility followed by transfer to a larger facility where more antivenom was given.

In this study, AKI was defined pragmatically as a composite endpoint of either requirement for dialysis **or**, in the absence of requirement for dialysis, a peak serum creatinine level of >120 μmol/l in men or >100 μmol/l in women *and* a pattern of rising serial creatinine consistent with AKI.

The clinical consequences of envenoming are listed in Table 1. AKI was extremely common, manifesting in 488 patients (71% of entire cohort). Of these 488, dialysis (predominantly haemodialysis) was required in 213 (31% of entire cohort), whereas the other 275 patients (40% of entire cohort) suffered a pathological rise in serum creatinine but did not need dialysis (median peak serum creatinine 245.5 μmol/l [IQR 332] in male patients, 260.5 μmol/l [IQR 322] in female patients). Female patients were 1.8 times more likely than male patients to develop AKI ($P < 0.01$). AKI developed more frequently in older patients, with odds ratio (OR) of 5.5 (11.4 for survivors) in those >64 years compared with those <15 years ($P < 0.01$).

Multivariate analysis (Table 2) showed that the time interval from bite to antivenom administration (irrespective of the initial dosage of antivenom) was the strongest predictor of subsequent AKI (OR 1.7 when antivenom was given at 1–2 hours compared

with 0–1 hour, $P < 0.05$; OR 3.2 at 2–3 hours compared with 0–1 hour, $P < 0.01$; OR 4.2 at 3–4 hours compared with 0–1 hour, $P < 0.01$; OR 12.4 at 4–5 hours compared with 0–1 hour, $P < 0.01$). This effect was observed across the 2 AKI subgroups as defined by dialysis requirement or serum creatinine rise without need for dialysis. Early administration of antivenom was also associated with shorter duration of coagulopathy (for patients receiving antivenom at 10 hours compared with those at 0–1 hour, $P < 0.001$).

The development of AKI was an important clinical event given that AKI was associated significantly with mortality. The overall mortality was 12.2% (84 of 686) among the entire cohort of 686 ERV cases. More specifically, mortality was 20.2% (43 of 213) in those who required dialysis compared with 10.2% (28 of 275) in those with AKI but did not require dialysis ($P = 0.002$), and 6.6% (13 of 198) in those who did not develop AKI ($P < 0.001$).

DISCUSSION

This study reveals the devastating scourge of snakebites in Myanmar. It highlights significant morbidity and mortality from ERV envenoming. The high rate of AKI (71%) was observed in a tertiary hospital caring for severely envenomed patients. The true rate of AKI consequent to all ERV bites may be lower, as not all patients require transfer to a tertiary hospital. Calculating the true risk of AKI requires accurate knowledge of snakebite incidence in the community. Our community-based survey of 2 rural townships in Mandalay indicated that the true incidence of snakebite in Myanmar may be twice as high as that derived from hospital data.[S1] Evidently, a nationwide survey of all levels of the health care system is required.

Our finding that female patients were 1.8 times more likely than male patients to develop AKI after ERV envenoming warrants further investigation. Factors such as smaller body mass relative to venom load, nutritional status, pregnancy, and anemia may contribute to this gender disparity.

The pathogenesis of AKI after ERV envenoming is incompletely known, but it is likely to be multifactorial, including microvascular fibrin deposition,[S2] direct nephrotoxicity,[S3] and hypotension.[6] Until more effective therapies become available, antivenom will remain the mainstay of treatment. Our finding that a shorter delay before antivenom had a better outcome is in broad agreement with 2 other reports based on smaller cohorts of patients.[3,S4]

Over the past 4 years, Australian, UK, and Myanmar colleagues have helped Myanmar become self-sufficient in antivenom production[8]; however, increasing the production of antivenom may not be enough to improve clinical outcomes. In response to our finding of an association between time to antivenom and AKI, the Myanmar Ministry of Health is reviewing its policies about distributing more antivenom to rural health care centers and township hospitals that are within closer reach of snakebite patients.

A limitation of this study is the lack of independent identification of snakes; the ERV cohort was based on assumed snake identity. Venom detection testing was not available, and very few dead snakes brought in by patients were kept for identification, although those that were available were predominantly ERVs. This limitation reflects the realities of clinical practice, where experienced clinicians must make pragmatic decisions about the likely culprit snake. In Mandalay Division of Myanmar, snakebite patients presenting with incoagulable blood are most likely to have ERV envenoming. The only other snakes causing this effect are green pit vipers (genus *Trimeresurus*), whose envenoming is unresponsive to ERV antivenom, and only very rarely results in AKI.

Although we had observed a beneficial effect of shorter time to antivenom, administration of 8 vials of antivenom compared with fewer than 8 vials did not correlate with decreased likelihood of AKI on either univariate or multivariate analysis. In this regard, several points are worth considering. First, this was an observational study, not a controlled clinical trial. Confounding factors, such as antivenom availability and clinical bias, may have influenced the initial antivenom dose. Antivenom rationing was common in rural health facilities; it was likely that higher antivenom dose was reserved for patients judged to have severe envenoming. Second, antivenom-specific factors such as unreliable storage cold chain and variable neutralizing potency may have limited its clinical efficacy. Efforts are under way to address these concerns and to determine the optimal initial antivenom dose through controlled clinical trials.

DISCLOSURE

All the authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary References.

Supplementary Methods.

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