SNAKEBITE IN KWAZULU-NATAL

THE BURDEN OF DISEASE AND PREDICTION OF RISK OF ADVERSE OUTCOMES

DARRYL ROSS WOOD

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Thesis submitted in fulfilment of the requirements for the degree of Doctor of Philosophy in the School of Clinical Medicine, University of KwaZulu-Natal.

Supervisor

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PREFACE

Of 3496 species of snake identified worldwide, approximately 600 are venomous. Snakebite constitutes a serious and neglected public health problem in much of the developing world, and has been labelled a “neglected tropical disease”. In South Africa there are some 38 venomous species, of which approximately half pose a significant threat to humans. Snakebite is of particular importance in the subtropical coastal belt in the north-eastern regions of KwaZulu-Natal.

There has been little systematic research into snakebite in South Africa or indeed in much of the developing world. The incidence is not precisely known, and much of the evidence on which treatment is based is anecdotal. The studies reported in this dissertation are intended to reinforce the scientific basis for the management of snakebite, and therefore enable better and more appropriate therapeutic and public health responses to the problem of snakebite.

DECLARATION

I, DARRYL ROSS WOOD declare that:

i. The research reported in this dissertation, except where otherwise indicated, is my original work.

ii. This dissertation has not been submitted for any degree or examination at any other university.

iii. This dissertation does not contain other persons' data, pictures, graphs or other information, unless specifically acknowledged as being sourced from other persons.

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SUPERVISOR Prof Richard Hift:

SIGNED Dr Darryl Wood)

3 February 2016

DEDICATION

This thesis is dedicated to Maya Cresley Wood who inspires me every day. Also to my wife, Dr Paula Sommer, whose support, patience and council has been my ballast.

ACKNOWLEDGMENTS

I express my great appreciation to my supervisor Prof Richard Hift who patiently mentored and guided me through this thesis. His expertise and skill in the field of research and writing has unquestionably enhanced my ability to better conduct research.

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ABBREVIATIONS

ATI	Active treatment intervention
KZN	KwaZulu-Natal
SAVP	South African Vaccine Producers
ZSSS	Zululand Snakebite Severity Score

PAGINATION AND REFERENCING

The pages of the dissertation are numbered consecutively at the bottom of each page. Work presented in manuscript form is additionally numbered separately, for each manuscript, in the top right corner.

Each manuscript is separately referenced thus [1]. The references are gathered together towards the end of each manuscript. The references for the introductory and concluding chapters are numbered thus **[1].** The bibliography is found at the end of the dissertation.

ABSTRACT

BACKGROUND

The total number of snakebites per annum in KwaZulu-Natal (KZN) is unknown. Yet it is believed that the burden that snakebites place on hospitals in areas with a high incidence of snakebite is significant. There are no official snakebite guidelines in South Africa or KwaZulu-Natal. The result is non-uniform management practices and in many cases inappropriate prescribing of antivenom, which may potentially be harmful given a high rate of allergic reactions to antivenom. In order to standardise practice along evidence-based lines, it is important to identify factors predictive of a poor outcome so that treatment can be appropriately targeted at those individuals.

AIMS

1. To determine a figure for the annual incidence of snakebite, identify regional variations in incidence and estimate the burden of snakebite on public hospitals in the north-eastern province of KwaZulu-Natal, an area in which snakebite is endemic.
2. To report a five-year prospective experience with snakebite in a highly endemic area of South Africa and to identify factors predictive of severity.
3. To develop and validate a severity scoring system to facilitate the management of snakebite in South Africa by allowing early identification of patients at increased risk of a severe course, and thereby develop an improved algorithm for the management of snakebite.
4. To determine the site of expansion accounting for the swelling in patients bitten by a cytotoxic snake species, in particular to distinguish between muscle compartment swelling and superficial swelling, and to determine the clinical utility of bedside ultrasonic examination as a potential tool for identifying patients with possible compartment syndrome.

METHODS

The work is reported as four sub-studies, using a selection of methodologies appropriate to each, which are fully described in Chapters 2-7.

In order to determine incidence of snakebite, we applied a novel method whereby incidence was extrapolated from antivenom supply data provided by the central provincial pharmacy depot, with the appropriate conversion factor being determined from a stratified a sample of 6 hospitals.

We analysed prospectively captured data on all patients admitted to Ngwelezane Hospital's Emergency Department from September 2008 to December 2013 with a diagnosis of snakebite. Using the need for an active treatment intervention (ATI), which we defined as antivenom administration or surgical intervention as a proxy for severity, we analysed our data for factors present on admission which were predictive of severity. In a subsequent study, we developed a severity score on a cohort of patients, which was then validated in a separate and subsequent cohort of patients.

We developed a methodology for the assessment of depth of bite in patients bitten on a limb whereby the ratio of the thickness of the deep muscle compartment and the subcutaneous compartment of the bitten limb, measured by bedside ultrasound, were expressed proportionally, and compared with the ratio on the unaffected limb. This information was then used to identify the major site of swelling.

RESULTS

Incidence

We estimated that 11% (95% CI: 8-14%) of snakebite presentations to hospital resulted in the administration of antivenom. By extrapolation, the overall incidence for KZN was 16/100 000. There was wide geographic variation, with the highest incidence, at 82/100 000 in the subtropical north east of the province. The estimated annual cost of snakebite in KZN was between USD 1 135 782 and USD 2 877 314.

Analysis of a case series and prediction of severity

879 cases were analysed. Envenomation was identified in over two thirds of admissions. Cytotoxic snakebites accounted for 98% of envenomations. Only 4 cases of haemotoxic bleeding and 5 cases of neurotoxicity were admitted. Although we demonstrated a significant correlation between severity and prolonged INR, reduced platelet count, haemoglobin, reduced or elevated leucocyte count and elevated serum urea. However, their use as predictors of severity was limited by poor sensitivity and specificity. Clinical factors correlating with severity were the paediatric age group and a delayed presentation to hospital.

In the prospective study, 146 of 879 snakebite admissions in the development cohort and 40 of 100 in the validation cohort reached the primary end point of an ATI. Six predictors of risk for ATI were identified from the development cohort: age <14 years, delay to admission >7 hours, white cell count > $10x10^9$ cells/l, platelet count<92 $x10^9$/l, haemoglobin <7.1 g/dl, INR >1.2. Each risk predictor was assigned a score of 1; ROC curve analysis returned a value of more than 4 out of 6 as the optimal cut-off for prediction of an ATI (AUC 0.804; 95% CI 0.758-0.84). Testing of the score on the validation cohort produced a sensitivity of 22.5% and a specificity of 96.6%. The PPV and NPV were 81.8% and 65.2% respectively.

Ultrasonic determination of the site of swelling in cytotoxic envenomation

The majority of bites were in the upper limb (27/42). Tissue expansion was noted in both the sub-cutaneous and muscle compartments of the envenomed limbs. The site of swelling was predominantly in the subcutaneous tissues, while swelling in muscle compartment was limited (the mean expansion coefficient for subcutaneous tissues was 2.0 (CI: 1.7-2.3) versus 1.06 (CI: 1.0-1.1) respectively). The difference between the groups was significant (P<001). One case, confirmed as compartment syndrome, showed marked swelling in the muscle group and stood out as a clear outlier in terms of the expansion coefficient.

CONCLUSIONS

The burden of snakebite is substantial, and is felt unequally across the province. Furthermore, we propose that our method may be used to estimate the incidence of other

diseases treated with a standard regimen and for which incidence figures are otherwise unknown.

Two-thirds of patients who present to hospital with snakebite in north-eastern South Africa will have symptoms of envenomation, with the overwhelming majority manifesting cytotoxicity. Bites by neurotoxic and haemotoxic species are rare. We have identified a number of factors which may potentially be of value in predicting severity, but which are on their own of insufficient accuracy to be reliable.

Basic ultrasound techniques may be used to identify the site and degree of tissue swelling from cytotoxic envenomation. It is a non-invasive, painless procedure that can assist the clinician to assess the injured limb and may also be of benefit to monitor the progression of swelling.

Our scoring system, which we propose to name the Zululand Snakebite Severity Score (ZSSS), is a useful adjunct to clinical assessment in managing snakebite. A patient with a positive result has an 80% probability of progressing to the point where an ATI is indicated. Its value is greatest in those patients who fall in the mild to moderate clinical category. This score now requires validation on a wider scale across South Africa, to determine its accuracy in areas other than those in which it was tested.

CHAPTER 1

INTRODUCTION

INTRODUCTION

CLINICAL AND DEMOGRAPHIC ASPECTS OF SNAKEBITE

Snakebite as a global public health problem

Snakebite has been labelled the "forgotten tropical disease" by the World Health Organization (WHO): indeed, snakebite was only added to the WHO's list of neglected tropical disease as late as 2009 **[1]**. It was subsequently removed from this list in 2015, resulting in urgent calls for its status as a neglected tropical disease to be restored **[2]**. The burden of snakebite rests on the tropical and subtropical regions of the world. It is estimated that 1.2 to 5.5 million people are victims of snakebite every year, 1 million of whom are in sub-Saharan Africa **[3-5]**. Other high incidence regions include the Indian subcontinent (121,000 snakebites), Southeast Asia (111,000 snakebites) and Latin America with a conservative 81,0000 cases annually **[5]**. Crude mortality estimates suggest 20,000-125,000 deaths worldwide from snakebite annually, 10,000- 30,000 occurring in Africa **[1,3,4]**; more recently, a figure of 200,000 deaths annually has been put forward **[2]**.

The morbidity from snakebite is significant with limb injury or loss having profound effects on victims' subsequent productivity and lifestyle. One estimate quotes upwards of 400 000 amputations due to snakebite worldwide **[1]**. Snakebite has also been labelled the "disease of poverty' **[6]** affecting populations who have poor resources and are politically impoverished; these factors contributing to the neglect of this disease by healthcare authorities **[7]**.

The majority of snakebite victims are agricultural field workers and children who reside in rural tropical environments **[8]**. Snakebite has also been seen as an occupational disease, particularly in areas where young agricultural workers are at risk as they encounter snakes in the course of farming activities; the morbidity consequent upon snakebite fuels the cycle of poverty by negatively impacting on the victims' ability to work **[7,9,10]**. A figure of 2 million disability adjusted life years (DALYs) loss per year for sub-Saharan Africa has been suggested **[8]**.

Venomous snakes in South Africa

South Africa has over 38 venomous snake species and about 16 species are classified as dangerous, able to inflict potentially limb- or life-threatening injuries. The two snake species most commonly responsible for serious snakebites in the north-eastern region are the puff adder (*Bitis arietans)* and the Mozambique spitting cobra *(Naja mossambica*), both with predominantly cytotoxic venom. Other snakes responsible for severe bites include further species with cytotoxic venom: the berg adder (*Bitis atropos*), night adder (*Causus rhombeatus*), horned adder (*Bitis caudalis*), gaboon adder (*Bitis gabonica)*, southern stiletto snake (*Atractaspis bibronii*) and the rinkhals (*Hemachatus haemachatus*); those with neurotoxic venom including the forest cobra (*Naja melanoleuca*), Cape cobra (*Naja nivea*), snouted cobra (*Naja annulifera*), black spitting cobra (*Naja nigricincta woodi*), black mamba (*Dendroaspis polylepis*) and green mamba (*Dendroaspis angusticeps*); and two species with haemotoxic venom: the boomslang (*Dispholidus typus*) and vine snake (*Thelotornis capensis*) **[11]**. The more important of these are illustrated in Figure 3 at the end of this chapter. The pictures presented were taken by the author and by the renowned herpetologist Johan Marais (permission granted).

Snakebite in South Africa and KwaZulu-Natal

When economically underdeveloped populations engaged in subsistence farming coexist with venomous snake species it is inevitable that snakebite will constitute a serious problem. The subtropical provinces of South Africa such as Limpopo and KwaZulu-Natal (KZN) have both these elements and reports of snakebite are common. Our experience with snakebite distribution in KZN suggests a large variation in snakebites from a reported high number occurring in the low lying coastal areas to a low number of cases in the high lying areas bordering on the Drakensberg (Chapter 3). Other regions such as the northern and western Cape also report snakebite but the incidence appears to be low. This highlights the extreme variation in the incidence of snakebite over even relatively short geographic distances, rendering large-scale statements on incidence, such as that of Kasturiratne *et al.* **[5]**, relatively meaningless at local level even as they provide a broad overview of the problem.

Research on snakebite in South Africa has been sparse and sporadic. The majority of studies have been done in the provinces of KZN and Limpopo. Doctors interested in the topic have sporadically done this research over the past few decades using descriptive observational methods. Snakebite is not a notifiable disease in South Africa, resulting in poor data collection with no accurate statistics on the number of bites or the geographical distribution of cases. International evidence suggests that many patients with snakebite do not present to health care facilities but rather seek medical attention from traditional healers **[12]**. The information on snakebites in South Africa is primarily from studies done in health care facilities and there is a shortage of community-based studies. These research data may underestimate the true burden on communities. One study in KZN showed an incidence of 44.5 bites per 100,000 population from hospital records versus 58.1 bites per 100,000 using hospital and community data **[13]**. As a result of these factors the burden of this disease on health care and the cost to healthcare is not known with any accuracy. Our experience is that most patients with significant envenomation signs and symptoms do present to a health care facility at some point, even after seeking treatment from traditional healers, though evidence to support this statement is lacking.

The demographics of snakebite in KwaZulu-Natal

In one of the earliest South African studies, Christensen **[14]** described a seasonal distribution to snakebites in South Africa, the warmer summer months having the highest number of snakebite while very few were noted in the winter season. The lower limb and feet were the commonest bite sites followed by the upper limb. There was equal distribution of bites between males and female subjects. Cytotoxic envenomation was much more prevalent than neurotoxic or haemotoxic envenomation. He showed a higher mortality rate among children than adults. Only 19.3 % of patients were given antivenom for severe envenomation. He reported an incidence of anaphylaxis induced by antivenom in this paper of 0.3%, which was much lower than that described in later studies. Subsequent research has more or less mirrored his findings. An adverse conclusion which can be drawn from this is that little has been achieved in snakebite prevention strategies while treatment practices remain essentially unchanged **[13,15-18]** (Table 1). It is apparent that the overwhelming majority of snakebite (over two thirds) cases occur in the summer months that are hot, humid and have a high rainfall **[15-17]**. Patients from rural areas practising

subsistence farming or who travel distances in open country for work purposes are at higher risk for snakebite. The gender distribution is essentially equal. Children are particularly vulnerable to snakebite and between 20 and 40% of all envenomation is in this group **[13,15,16,18]**. The incidence of snakebite from these studies appears to be between 28/100,000 and 96.5/100,000 **[13,15,17,19]**.

Clinical presentations and outcomes

It is difficult for non-experts to identify the offending species in most cases of South African snakebite **[7,14,15,17]**. Thus doctors adopt a syndromic approach to managing snakebites, as proposed by Blaylock **[20]**. Patients with snakebite in South Africa present with one of three syndromes, dependent on the species responsible for the bite. *Painful progressive swelling* is caused by cytotoxic envenomation primarily from the adders and spitting cobras. *Progressive weakness* is caused by neurotoxic envenomation primarily from the cobra and mamba species. *Bleeding* is caused by haemotoxic envenomation primarily from the boomslang and vine or twig snake. Venoms are essentially complex proteins and enzymes, and more than one syndrome may be present following envenomation. Examples of this are swelling that may occur in some of the neurotoxic cobra bites or bleeding that may occur with severe adder bites. Figure 1 represents an adaptation of Blaylock's syndromic approach to snakebite management and is currently the standard guideline at Ngwelezane Hospital, the main referral centre in the north-eastern region of KZN.

The commonest presentation following snake envenomation is cytotoxic painful swelling (Figure 4). More than 80% of envenomations in KZN are from species with cytotoxic venom **[15-17]** causing varying degrees of swelling and necrosis. The venom causes immediate tissue damage and severe cases limb loss and even death may occur. Cytotoxins (phospholipase A2 and metalloproteinases) damage cell membranes and create pores in capillary endothelial layers **[21]** resulting in pain, swelling, bruising and necrosis; the ongoing process may persist for days. This group of patients poses a clinical conundrum for doctors since predicting the eventual outcome of the progressive swelling which follows envenomation is difficult. Though significant swelling, blistering and necrosis, placing the patient in the severe group at initial presentation, in more moderate swellings, the swelling

Table 1: Demographic and clinical results from earlier studies in KZN

Study	Sample number	Bites in Summer (%)	Male (%)	Child (%)	Lower limb bite (%)	Antivenom	Ana-phylaxis (%)	Incidence /100 000	Mortality /100 000
Christiansen (1981)	2553	>66%	45%	No data	74%	20%	0.3%	No data	(3%)
Coetzer and Tilbury (1982)	161	68%	43%	43% (<12 yrs)	84%	10%	19%	97	0.23
Blaylock (2004)	333	75%	50%	No data	83%	4%	42%	31	O,3
Sloan *et al.* (2007)	691	76%	53%	21% (< 10 yrs)	88%	10%	No data	44.5	0.08
Wood *et al.* (2009)	243	66%	51%	21% (<10 yrs)	No data	9%	38%	46	0

may progress over time, placing the patient at increasingly high-risk of an adverse outcome. Thus the dynamic clinical component of swelling progression can be used as a guide to

grade the severity of envenomation (Figure 4).

The commonest presentation following snake envenomation is cytotoxic painful swelling. A major concern in cytotoxic envenomation is involvement of the muscle bed. Diagnosing an intramuscular compartment syndrome is critical for saving an envenomed limb, however, the effects of the venom on subcutaneous layers can mimic a compartment syndrome without the muscle being affected. Compartment syndrome following snakebite is in fact thought to be rare **[22]**. Of the studies done in KZN, Blaylock **[17]** reported 4 cases of compartment syndrome in 333 patients and Wood *et al.* **[16]** reported 4 cases in

Figure 1: Current guideline for the syndromic management of snakebite in north-eastern KwaZulu-Natal, adapted from Blaylock **[20]**

243 patients, while none were described by Coetzer and Tilbury **[15]**. While the consequences of a missed compartment syndrome are devastating, the morbidity associated with an unnecessary fasciotomy is substantial. The decision to perform a fasciotomy may be difficult but is critical **[23-27]**. Early antivenom is effective for cytotoxic envenomation and can significantly reduce the progression of swelling and the extent of necrosis. However, the current South African polyvalent antivenom does have significant adverse effects, including life-threatening anaphylaxis. Correctly balancing the benefits versus risks of antivenom constitutes a serious challenge when treating snakebite **[14,28-37]**.

Very few cases of pure haemotoxic or neurotoxic snakebite presentations are encountered. Both haemotoxic bleeding and neurotoxic weakness are regarded as a severe manifestation of envenomation and should be treated with antivenom immediately. The boomslang is a back fanged snake with a very potent haemotoxin that causes a disseminated coagulopathy **[38,39]**. It is generally a timid tree dweller that seldom bites humans and cases are extremely rare. The only effective treatment is the South African Vaccine Producers (SAVP) boomslang-specific monovalent antivenom. Neurotoxic result primarily from elapid species such as cobras and mambas and the mortality is high if the patient is not treated with the SAVP polyvalent antivenom which is effective. However, less than 1% of cases presenting to hospitals are due to these species **[14-16]**.

Children are particularly vulnerable to snakebite and appear to have poorer outcomes than adults. A greater venom-to-body size ratio may explain the more profound effects seen both systemically and to the local tissues in children **[40]**. A correlation has been proposed between size of the injecting snake and severity of cytotoxicity **[41,42]**; as a consequence, it might hold that a smaller victim would be subject to greater toxicity. Few studies specifically target children, who are normally included in general surveys biased towards adults **[43]**; when studies specifically targeting children are conducted **[40,43,44]**, comparison with adult outcome is often not possible. More children require antivenom than adults, while the rate of anaphylaxis is significantly higher **[16]**. There also appears to be a higher mortality in children than adults **[14,18,45]** but larger studies are required to confirm this assumption. Other reports however have not found such a correlation **[46]**. Surprisingly, a meta-analysis of snakebite in Europe was unable to demonstrate that children are more severely affected than adults **[47]**. The dose of antivenom required to neutralize venom-derived toxins is proportional to the potency and volume of the injected

venom, not the body weight of the patient. Consequently children require the same volumes of antivenom as adults **[39]**, with a higher risk of adverse effects. Irrespective of risk, management of envenomed children is particularly challenging, particularly where facilities are geared towards the treatment of adults.

The clinical dilemma that clinicians in South Africa face is making the appropriate decision for prescribing antivenom, considering the significant risk for possibly life-threatening adverse reactions. For most doctors accurately assessing snakebite is difficult and the decision to give antivenom is often made without using objective tools. In an attempt to assist doctors various scoring systems have been published elsewhere, such as the Snakebite Severity Score (SSS) proposed for the United States **[48,49]** which essentially assigns points for clinical assessment and coagulation parameters. However, this scoring system is only validated in North American crotalid and copperhead snake species. An objective system to evaluate snakebite patients in South Africa has not been published or validated but is sorely needed.

Antivenom therapy

The mainstay of treating snake envenomation is antivenom. Antivenom is derived from animals, usually horses or sheep into venom antigen exposure is injected resulting in the production of neutralizing antibodies. Purification processes vary but plasma fractionation and protein digestion using pepsin or papain are commonly used **[35]**. Depending on the type of the fractionation process used, 3 types of antivenoms are produced; whole IgG, (usually with ammonium sulphate or caprylic acid), $F(ab')_2$ fragments (using pepsin degradation) and monovalent Fab using (using papain digestion) **[33]**. The costs of producing antivenom increase exponentially with the additional preparation and digestion processes and are in many products omitted on the grounds of cost. Simpler and cheaper purification processes result in a cruder preparation and an increase in the incidence of adverse reactions such as anaphylaxis.

The difficulties in mobilizing government and the pharmaceutical industry to ensure a sufficient supply of vaccine in parts of the world such as sub-Saharan Africa and Asia are understood, and a programme has been launched to encourage the supply of modern, safe and effective antivenoms and to ensure a stable supply as part of an integrated approach to

this neglected tropical disease **[1,7,50]**; yet the shortage of vaccine in Africa in particular remains acute **[51-53]**. In Asia, shortage of vaccine is not an issue as the vaccine is produced in sufficient quantities by Indian manufacturers. The major problem lies in proper routes of distribution, logistics and education of doctors, patients and communities in its use **[54]**. This contrasts with sub-Saharan Africa where there are major deficiencies in production. It has been estimated that the number of effective antivenom treatments available for snakebite victims in sub-Saharan Africa may be as little as 2.5% of the projected need, though some new products are indeed under development **[55,56]**.

The availability of antivenom in Africa has declined significantly over the past few decades. **[51-53]**. Recent reports suggest that less than 20,000 vials of antivenom are supplied for snakebite envenomation in Africa annually compared to more than 200,000 vials 25 years ago, currently a very small percentage of what is required **[3,4,55]**. More in sub-Saharan Africa recently there has been some increase in antivenom production, from 54,000 complete treatments (227,400 vials) in 2007 to 83 000 complete treatments (377,500 vials) in 2010/2011. The target is to provide treatment to 600,000 patients with snakebite **[55]**. South Africa has not benefited from the many recent advances in vaccine development arising from the study of venomics and improved manufacturing practical protocols **[31,57,58]**. Indeed, in common with most Indian-produced vaccines such as those routinely used in south Asia **[54]**, the vaccine has never been subjected to independent formal evaluation and the protocols for its use are not firmly evidence-based.

The Global Snake Bite Initiative **[50]** has been created to raise public awareness of the scale of the problem, develop sustainable and workable solutions within regions, support the WHO's Department of Neglected Tropical Diseases to develop guidelines for the production, regulation and control of antivenoms and to support research to better understand the epidemiology of snakebite, injury mechanisms inflicted on victims and optimize treatment interventions, and active research to develop better antivenoms continues **[30]**.

Adverse reactions to antivenom

Early adverse reactions are essentially an allergic reaction of the host to the components of the antivenom. The severity of the reaction ranges from a mild urticarial skin rash to life-

threatening anaphylaxis with circulatory collapse. *In vitro* studies indicate that the process is one of immune complex aggregation and deposition following complement activation in response to antivenom exposure **[35]**. IgE mediated allergic reactions do not appear to be implicated. In addition, a pyrogenic reaction in response to contaminants and protein debris in the antivenoms is common. Anaphylaxis may also be related to the volume of these complement activated protein aggregates, as there appears to be a correlation between the volume of administered antivenom and the probability of an adverse reaction. Antivenoms purified using simple processes with a higher yield of proteins are more likely to cause reactions then more than those produced with more intensive fractionation **[35]**.

The polyvalent antivenom in use in southern Africa, produced by South African Vaccine Producers (Pty) Ltd (SAVP), is a partially purified equine-derived antiserum, first introduced in 1928 and active against the venoms of two species **[14]**, which has been modified at intervals by the addition of further valences, such that it is currently marketed as being active against the venoms of ten species **[59]**. It has however not been improved in over 30 years. By modern standards, the degree of purity and specificity is not acceptable, as evidenced by the very high rate of anaphylaxis. From the published data in KZN an average of about 9% of all envenomations are treated with antivenom (Table 1). The rate of anaphylaxis from the polyvalent antivenom is high. Recent studies have described the rate to be about 40% which is higher than previously reported. The highest reported incidence of anaphylaxis from the South African polyvalent antivenom is 76% **[60]**. The rate of anaphylaxis with Indian-manufactured polyvalent antivenoms that are used in India and Sri Lanka is similar, ranging from 40-81% **[34]**, although one study reported a low anaphylaxis rate of 8% **[61]**. A study from Bangladesh reported an anaphylaxis rate of 64.5% with a polyvalent antivenom **[62]**. Early adverse reactions to South American polyspecific antivenoms range from 17%-73% **[63]**.

The need for more purified and specific antivenoms is clear but the cost of producing these products is essentially prohibitive in the developing world. The Antivenin Crotaline Polyvalent used to treat north American crotaline snakebites is composed of IgG antibodies derived from horse serum. The rate of adverse reactions for this antivenom is reported between 23%-56%. A sheep-derived, and more purified Fab fragment antivenom (FabAV) is also available and has only a 14.3% rate of adverse reactions **[64]**. New antivenoms for Africa are being investigated and produced in response to the shortage of antivenom

supply. Products such as the Pan African polyvalent antivenom (IgG derived from horse serum) and Antivipmyn® polyvalent antivenom ($F(ab)_2$ horse derived) are being developed against extended range of snake species (genera include *Echis, Bitis, Naja* and *Dendroaspis*) that occur across Africa **[56,65]**. The long term plan would be to produce large quantities of an effective and cost effective broad spectrum polyvalent antivenom that has a low risk for early adverse reactions.

Strategies to prevent or reduce the risk for anaphylaxis following antivenom are controversial. Pharmacological prophylaxis, pretesting patients with antivenom and adjusting the rate of antivenom infusion are the main strategies to reduce anaphylaxis. The traditional pharmacological approach is to predose the patient with adrenaline, antihistamines and corticosteroids. The available evidence supports the efficacy of pre dose adrenaline in reducing anaphylaxis while both antihistamine and corticosteroids have shown no benefit **[28,34,36,66]**. The rate at which the antivenom is infused **[67]** nor its timing **[66]** do not appear to influence the risk for anaphylaxis. Pretest sensitivity testing with antivenom has proved to be unreliable in predicting early reactions to antivenom and no longer advocated **[37,68]**. However, even in the absence of evidence supporting practices such as administration of hydrocortisone, many doctors in South Africa continue to prescribe and treat patients inappropriately with these drugs.

THE CURRENT PROJECT

Problem statement

KwaZulu-Natal has regions in the north-east of the province (Figure 2) that are subtropical in climate predisposing the large essentially rural population to tropical diseases. Malaria, dysentery, bilharzia and cholera are some of these diseases. Large-scale eradication programs provincially, nationally and regionally have had a dramatic effect in reducing the burden of diseases such as malaria. In contrast, snakebite is a tropical disease that tends to be forgotten but has a significant impact on the local population. Snakebites are a reality for the population of most of KZN and bites are prevalent in the northern coastal areas. Yet little has been done to fully understand and manage this disease. Certainly, the pattern and

incidence of snakebites has not changed over the past few decades while treatment and management strategies have seen minimal progress.

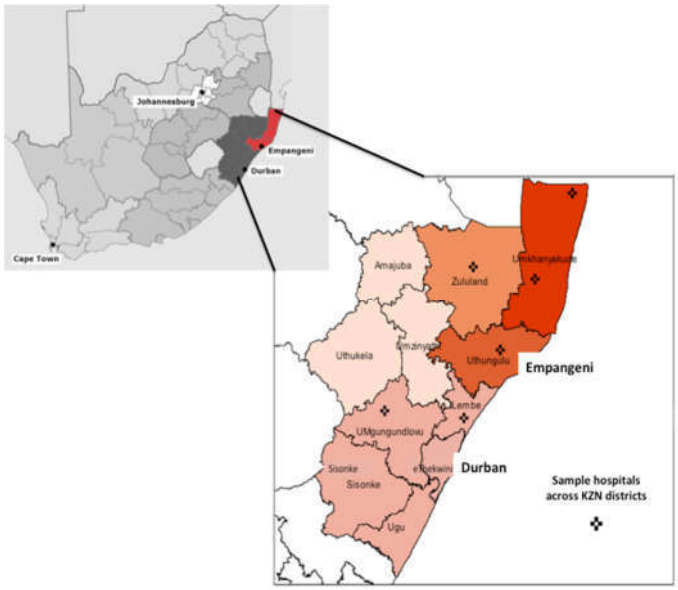

Figure 2. Administrative map of KwaZulu-Natal Province in the context of South Africa showing health districts. The three regions in the far north east have the highest incidence of snake bite and most of the work of this dissertation is drawn from that area

Snakebite is not a notifiable disease, hence there are essentially no provincial and national statistics on the number of cases and mortality rates. The assessment and management of snakebites by doctors is highly variable and usually depends on the experience of the clinician. Currently there is no nationally agreed or officially sanctioned protocol on management, in contrast to a disease such as malaria that is the focus of a national strategy on prevention and treatment, and for which regularly updated guidelines and protocols are issued. The success of such campaigns in South Africa is evident by the marked decrease of malaria cases from 64 622 in 2000 to 8066 in 2010. The largest decreases were noted in KZN, indicating the success of strategic programs in this province **[69]**.

We have noted that over the summer months the burden of snakebite on hospitals in some of the regions in KZN is significant. For instance, at Ngwelezane Hospital in the northeast of the province, as many as 200 new snakebite cases may be admitted over a 4-month period, equating to approximately 2 cases per day. Snakebites are responsible for about

10% of all emergency admissions over the summer months. The health burden placed on the Emergency Department and the hospital is significant. Yet there is no official guidance on how to manage this disease effectively. Possibly it is the lack of understanding snakebite as a disease rather than the traditional perception that snakebite is an unfortunate chance encounter resulting in an injury. Quantifying the burden of this neglected disease and identifying areas where interventions will have an impact on patient care and outcomes is sorely needed.

Aim of the study

The aim of the present study was to investigate the prevalence, demographics and clinical consequences of snakebite, particularly with reference to factors predictive of a more severe outcome, in order to provide a basis of rigorously obtained data which would allow for contextualisation of snakebite as a public health problem in KZN and the modification and improvement of treatment recommendations and protocols in order to improve clinical outcomes.

Objectives

The study had the following objectives:

1. To determine a figure for the annual incidence of snakebite, identify regional variations in incidence and estimate the burden of snakebite on public hospitals in the north-eastern province of KZN, an area in which snakebite is endemic.
2. To report a five-year prospective experience with snakebite in a highly endemic area of South Africa and to identify factors predictive of severity.
3. To develop and validate a severity scoring system to facilitate the management of snakebite in South Africa by allowing early identification of patients at increased risk of a severe course, and thereby develop an improved algorithm for the management of snakebite.
4. To determine the site of expansion accounting for the swelling in patients bitten by a cytotoxic snake species, in particular to distinguish between muscle compartment swelling and superficial swelling, and to determine the clinical utility of bedside

ultrasonic examination as a potential tool for identifying patients with possible compartment syndrome.

Study design and methodology

The work is reported as four sub-studies, using a selection of methodologies appropriate to each, which are fully described in Chapters 2-7.

STRUCTURE OF THE DISSERTATION

Chapter 1

Introduction, literature review, aim and objectives and outline of methodology.

Chapter 2

This chapter represents work performed by the candidate prior to the commencement of the doctoral project, and served as a pilot study on which the prospective research was based.

This was published as: *Wood D, Webb C, DeMeyer J. Severe snakebites in northern KwaZulu-Natal: Treatment modalities and outcome.* S. Afr. Med. J. 2009; **99**: 814-8.

Chapter 3

Estimating the burden of snakebite on public hospitals in KwaZulu-Natal, South Africa.

This chapter presents the literature review, methodology, results and discussion for Objective 1. This work was published as: *Wood DR, Hift RJ, Sartorius B. Estimating the burden of snakebite on public hospitals in KwaZulu-Natal, South Africa*. Wilderness and environmental medicine 2016; **27**:53-61.

Chapter 4

This chapter presents the literature review, methodology, results and discussion for Objective 2. This work was published as: *Wood D, Sartorius B, Hift R. Snakebite in north-*

eastern South Africa: clinical characteristics and risks for severity. South African family practice 2016; **58**: 62-67.

Chapter 5

Classifying snakebite in South Africa: Validating a scoring system.

This chapter presents the literature review, methodology, results and discussion for Objectives 2 and 3. The work is presented in manuscript form as *Wood DR, Sartorius B, Hift R. Classifying snakebite in South Africa: Validating a scoring system.* This paper has been accepted by the *South African Medical Journal* for publication.

Chapter 6

Ultrasound findings in 42 patients with cytotoxic tissue damage following bites by South African snakes.

This chapter presents the literature review, methodology, results and discussion for Objective 4. This work was published as: *Wood D, Sartorius B, Hift R Ultrasound findings in 42 patients with cytotoxic tissue damage following bites by South African snakes*. Emerg med J 2016; **33**: 477-81.

Chapter 7

Synthesis and discussion

References

FIGURES 3-5

Figure 3. Common venomous snake species in KwaZulu-Natal

Fig 3a. Mozambique spitting cobra**,** *Naja mossambica*

Fig 3b. Rinkhals, *Hemachatus haemachatus*

Fig 3c. Puff adder, *Bitis arietans*

Fig 3d. Gaboon adder, *Bitis gabonica*

Fig 3e. Boomslang, *Dispholidus typus*

Fig 3f. Forest cobra, *Naja melanoleuca*

Fig 3g. Green mamba, *Dendroaspis angusticeps*

Fig 3h. Black mamba**,** *Dendroaspis polylepis*

Figure 4. Clinical injuries from snakebite

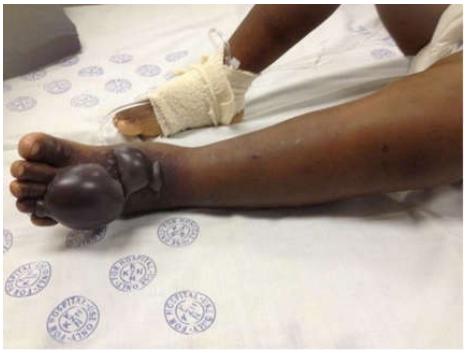

Fig 4a. Cytotoxic swelling and blistering of the leg

Fig 4b. Cytotoxic swelling of the forearm and hand

Figure 5. Antivenom and its consequences

Fig 5a. Four vials (40ml) polyvalent SAVP antivenom diluted in 200ml normal saline

Fig 5b. Boomslang specific antivenom

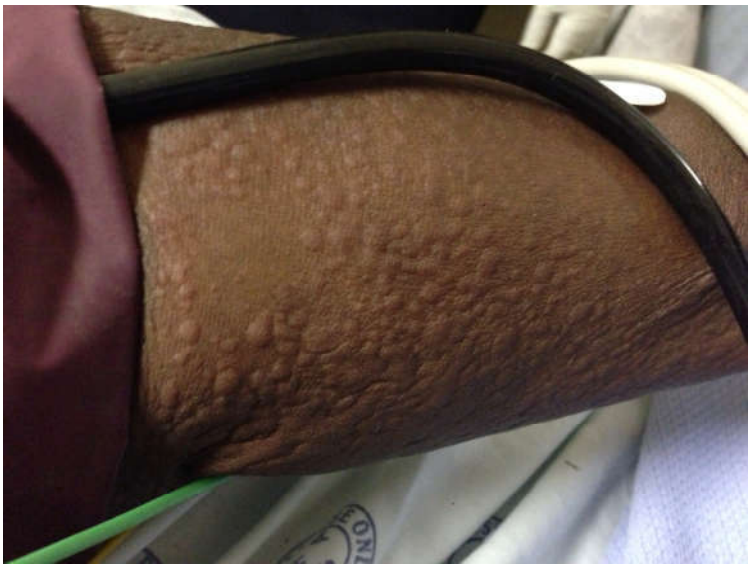

Fig 5c. Early adverse reaction: Urticaria post antivenom administration

CHAPTER 2

Severe snakebites in northern KwaZulu-Natal: Treatment modalities and outcomes.

Severe snakebites in northern KwaZulu-Natal: Treatment modalities and outcomes

Darryl Wood, Caroline Webb, Jenine DeMeyer

Objective. We aimed to study the outcomes of severe snakebites in patients admitted to Ngwelezana Hospital in north-eastern KwaZulu-Natal, the seasonal variations, and the effectiveness and complications of antivenom.

Design. A prospective observational outcomes study was conducted over one year (1 June 2007 to 31 May 2008). The study group was from the north-eastern KwaZulu-Natal region of South Africa, with a population of approximately 3 million people, and included all patients bitten by snakes and admitted to the Ngwelezana Hospital Emergency Medicine Unit (EMU). Departmental practice guidelines were documented and followed.

Outcome measures. End-points for patient outcomes included transfer from the EMU to the ward, discharge home from the EMU, and follow-up of patients who required surgery or ICU care.

Results. A total of 243 snakebite patients were recorded. The highest incidence was in the summer months; 46 (18.93%) patients experienced one or more severe complications; 29 (11.93%) patients received some form of definitive management in hospital; and 22 (9.05%) of the latter patients received antivenom. Antivenom was administered to more children than adults. Adverse reactions to antivenom were common: an allergic response occurred in 4 (15.4%) patients, and anaphylaxis in 6 (23.1%); the highest incidence occurred in the <10-year-old age group. No deaths were recorded.

Conclusions. Snakebites are common in the summer months in north eastern KwaZulu-Natal. Children are particularly vulnerable to snakebites and the effects of antivenom. Adverse reactions to antivenom are common. Severe snakebites that require antivenom should be managed in a hospital setting with advanced airway support. The syndromic approach to treatment is simple and effective.

S Afr Med J 2009; 99: 814-818.

Snakebites are common in the sub-tropical north-eastern region of KwaZulu-Natal. Several studies have investigated the epidemiology of snakebites in hospitals in rural Kwazulu-Natal.[1-3] We aimed to observe outcomes of severe snakebites in patients admitted to Ngwelezana Hospital. Seasonal variations of snakebites and the effectiveness and complications of antivenom were assessed.

KwaZulu-Natal and Mpumulanga have the highest incidences of snakebites in South Africa, with 24 - 34 per 100 000 people being bitten annually.[4] Less than 10% of snakes in southern Africa are potentially lethal; the reported snakebite mortality rate is 1 - 2%.[4] The snakes responsible for severe bites in the study region include: forest cobra (*Naja melanoleuca*), M'Fezi or Mozambique spitting cobra (*Naja mossambica*), Egyptian cobra (*Naja haje*), black mamba (*Dendroaspis polylepis*), green mamba (*Dendroaspis angusticeps*), boomslang (*Dispholidus typus*), vine snake (*Thelotornis capensis*), puff adder (*Bitis Arietans*) and Gaboon viper (*Bitis gabonica*).[2] The most commonly reported dangerous snakebites are from the M'fezi and puff adder,[2] while the notorious black mamba causes life-threatening neurotoxic envenomation.

Empangeni is a town in north-eastern KwaZulu-Natal. Ngwelezana Hospital is a 500-bed hospital situated in a semi-rural settlement outside Empangeni, and is the referral centre for 22 rural hospitals. It has an emergency medicine unit (EMU) where all snakebite patients are observed and treated.

Antivenom is manufactured by the South African Institute for Medical Research (SAIMR).[5] It neutralises active snake venom and is the definitive management for severe snakebite envenomation. Polyvalent antivenom is effective against most snakes that are likely to cause life-threatening envenomation in southern Africa, except certain adders, the boomslang and the vine snake. The SAIMR has produced two monovalent antivenoms for the haemotoxic boomslang and the saw-scaled viper.

The indications for antivenom use are listed in Fig. 1. Studies in Eshowe and Durban showed that up to 41 - 50% of patients experienced an adverse effect to antivenom use.[1,6] Acute anaphylaxis (e.g. hypotension, bronchospasm) is not dose-related and typically occurs 1 - 15 minutes after antivenom administration.[5] Milder allergic reactions such as urticaria and tachycardia can also be experienced. Serum sickness (urticaria, polyarthritis, mild fever and lymphadenopathy) is usually delayed by up to 7 - 12 days.[5,7] Test dosing with antivenom is no longer recommended.[8] Fig. 2 shows the guidelines for

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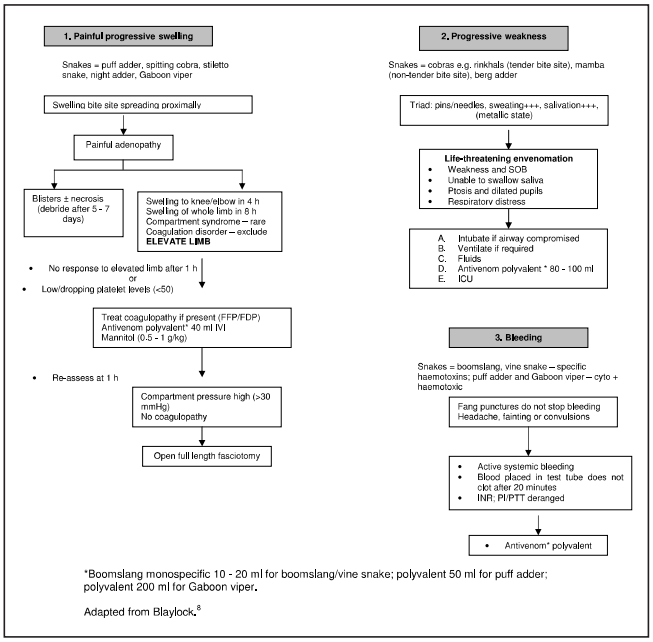

Fig. 1. Guidelines for the management of snakebites.

1. Severe life- or limb-threatening envenomation
2. Discuss with emergency medicine or surgical consultant before administering antivenom
3. Doctor with airway skills needed to assist (senior EMU doctor or anaesthetist)
4. Facemask oxygen; two large-bore cannulas (>18 G) with normal saline running
5. Monitor blood pressure, pulse and saturation
6. Resuscitation trolley and defibrillator on standby
7. Premedication: 1. IVI hydrocortisone 200 mg in adults; 4mg/kg in children at least 30 minutes prior to antivenom
   2. IVI phenergan 25 - 50 mg diluted in 10 × water in adults ; IMI (0.125 - 0.5 mg/kg) in children >5 years may be considered; avoid in children <5 years.
   3. IMI adrenaline 0.3 - 0.5 mg in adults; 0.01 mg/kg in children
8. 40 ml antivenom IV over 15 minutes (test dose not required)

*Repeat doses (1 - 4 vials) may be required every 1 - 2 hours if symptoms persist; larger doses may be required (up to 100 ml) in neurotoxic envenomation.

Fig. 2. Antivenom administration.

administering antivenom. The effectiveness of premedication with hydrocortisone, antihistamines and intramuscular adrenaline in reducing the risk of anaphylaxis is unknown.[8]

The dose of antivenom depends on the type and amount of venom injected rather than the weight of the patient. Children therefore receive the same amount of antivenom as adults. Further doses can be given and are titrated against the patient's response. Haemotoxic venoms tend to have a delayed onset.[2]

Practice guidelines adapted from Blaylock were used in this study.[8]

Methods

A prospective observational outcomes study from north-eastern KwaZulu-Natal, with a population of approximately 3 million people, was conducted over 1 year (1 June 2007 to 31 May 2008). All patients who were bitten by snakes and admitted to the Ngwelezana Hospital EMU were documented. Departmental practice guidelines were followed (Fig. 1). All snakebite patients from the immediate local area (Uthungulu) were included. Only those with severe symptoms from outlying referral hospitals were accepted for admission to the EMU.

The data were collated daily by two doctors working in the EMU. Endpoints for patient outcomes were:

- transfer from the EMU to the ward
- discharge home from the EMU
- follow-up and documentation of patient outcomes with severe progressive symptoms requiring surgery or ICU care.

All patients with suspected snakebites admitted to the EMU were included and confirmed by cross-reference with the admission logbook of the unit.

Every patient was reviewed by a senior doctor (principal medical officer, chief medical officer or consultant) within 12 hours of admission. The management guidelines classify envenomation symptoms as **painful progressive swelling, progressive weakness and bleeding**.[8] Patients with severe symptoms were observed for at least 12 hours, with regular documentation of the progression of swelling, neurological status, signs of bleeding and examination for compartment syndrome. Patients with an uneventful course were transferred to the ward. Patients with unconvincing snakebite symptoms (absence of fang marks or no local swelling) were discharged home following a period of observation and normal blood results. The causative snake was rarely identified as patients' herpetological knowledge was generally unreliable, and invariably the snake was not seen at the time of the bite.[2]

Severe complications associated with snakebites were categorised according to specific criteria:

1. **Rapid progressive swelling**. Swelling crossing 2 large joints within 4 hours or the entire limb by 8 hours following the snakebite. Snakebites that potentially compromised the airway were also included in this category.
2. **Compartment syndrome**. Following rapid progressive swelling, an increase in compartmental pressure resulting in microcirculatory arrest and vascular compromise to the limb.[6] Snakebites usually cause subcutaneous oedema without raised compartment pressures.[8] We did not measure compartmental pressures.
3. **Haematological disorder**. An international normalised ratio (INR) >1.5, haemoglobin <8.0 g/dl or platelet count $<50\times10^9$/l.
4. **Neurotoxicity**. Symptoms suggestive of neurotoxicity from envenomation typically include drowsiness or a depressed level of consciousness, limb weakness, sweating, vomiting, inability to swallow saliva, ptosis, blurred or double vision, and respiratory muscle paralysis.[4]

Snakebites are usually categorised according to the primary action of their venom into cytotoxic, haemotoxic and neurotoxic. However, many snakes inject a variety of toxic compounds that may cause more than one type of syndrome.[6] Patients with more than one type of severe complication had each one documented separately.

Antivenom administration was at the discretion of the consultant, according to departmental guidelines (Fig. 2). In all cases resuscitation equipment was on standby, in readiness for anaphylaxis. Hydrocortisone, antihistamine and adrenaline were given prior to the antivenom. The SAIMR polyvalent antivenom was diluted in saline and administered over a 15-minute period, with careful monitoring for allergic or anaphylactic responses.[5] An initial standard dose of 4 vials of antivenom was used, regardless of age, and repeated as necessary. Patients with neurotoxic snakebites typically required higher doses of antivenom; endotracheal intubation was considered in these cases owing to the risk of respiratory muscle paralysis. Adverse reactions to antivenom administration were classified as either allergic (mild response, most commonly manifested as pruritus, skin weals and an associated tachycardia) or anaphylactic (severe, potentially life-threatening systemic reaction). Patients who became hypotensive or experienced bronchospasm were classified as having an anaphylactic reaction. Only acute reactions were documented. Serum sickness was not investigated owing to the inability to follow up patients after discharge from the EMU.

Results

A total of 243 snakebite patients were recorded; 29 (11.93%) were referred from peripheral hospitals within the Ngwelezana catchment area. Most snakebites were recorded in January (Fig. 3) (peak of summer, with average daily temperatures of around 32ºC and high humidity levels). The data show a rising trend in snakebites in the summer months. The most common snakebite population groups were children and young adults; 137 (56.4%) were <20 years old (Fig. 4).

Most patients (81.1%) had mild symptoms. One or more severe snakebite complications were experienced by 46 (18.9%), as follows: haemotoxicity in 27 (58.7%); rapid progressive swelling in 18 (39.1%); compartment syndrome was diagnosed clinically in 4 (8.7%), but only one patient received a fasciotomy; and neurotoxicity in 3 (6.5%). All of them received antivenom. No patients died.

Twenty-nine (11.9%) patients received some form of definitive management; some received more than one, depending on complexity of the symptoms. Antivenom was administered to 75.9% of all patients who required definitive treatment; 22 (9.1%) received antivenom. Blood products (packed red cells, fresh-frozen plasma or platelets) were given in 6 cases; 3 required endotracheal intubation in the EMU (2 for severe neurotoxicity and 1 for anaphylaxis due to antivenom

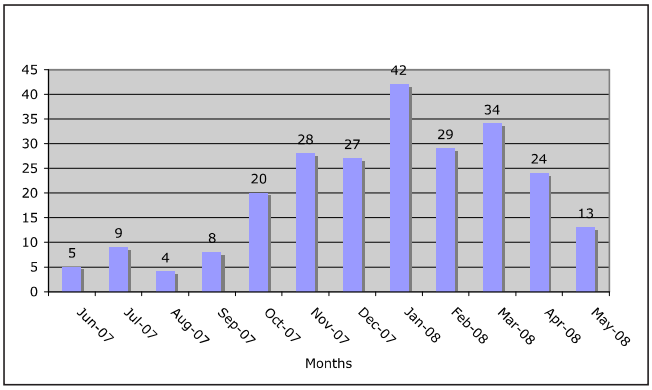

Fig. 3. Monthly distribution of snakebite patients.

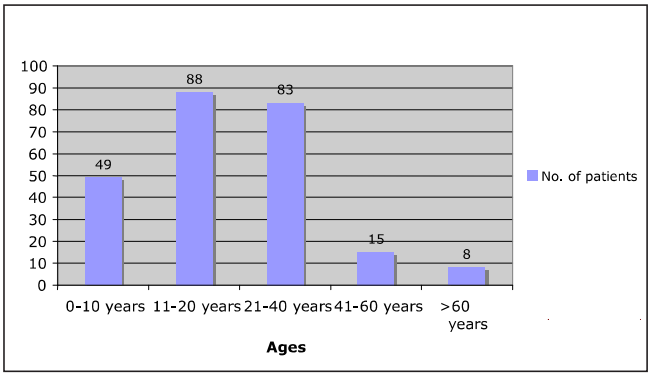

Fig. 4. Age distribution of snakebite patients.

administration); and 11 (4.5%) required surgery including debridement of necrotic snakebite wounds, amputation of affected limbs or digits, or fasciotomy. All 4 cases of clinically diagnosed compartment syndrome received antivenom. One patient required a fasciotomy.

Antivenom administration

Twenty-two patients were given antivenom; 4 received antivenom at their referral hospitals before admission to the Ngwelezana EMU. Half of the patients given antivenom at Ngwelezana came from referring hospitals. Only patients with complicated snakebites that could not be managed at the peripheral referring hospitals were sent to Ngwelezana Hospital for further treatment.

Antivenom was administered to more children than adults: 15 (68.2%) patients receiving antivenom were <20 years old (0 - 10 years: 8, 11 - 20 years: 7, ≥20 years: 7). The most common indication for antivenom administration was rapid progressive swelling (14 (46.7%) of patients), with haemotoxicity in 8 (26.7%) coming next. All 4 cases of clinical compartment syndrome received antivenom. One patient received antivenom for venom-related shock. Many patients met the criteria for more than one indication for antivenom administration.

The mean time to antivenom administration was 16 hours after the bite; this delay can be attributed to:

- lack of transport in rural areas
- transfer of patients from referring hospitals
- patients seeking advice from traditional healers before going to hospital
- prolonged observation of symptom progression in the EMU.

Adverse reactions to antivenom were common; only 7 (31.8%) patients received antivenom without any adverse reaction. An allergic response occurred in 4 (15.4%) cases and anaphylaxis in 6 (23.1%) (Table I). Two patients were transferred to the ICU: an adult male with neurotoxic snakebite symptoms, and a young girl with rapid progressive swelling, compartment syndrome and reperfusion injury. One patient was transferred to a tertiary hospital following an anaphylactic reaction to the antivenom.

The highest percentage of adverse reactions to antivenom occurred in the 0 - 10-year age group, while most adults (85.7%) experienced no complications (Table I). Of the 8 patients under the age of 10 who received antivenom, only 2 (25%) had no adverse reaction. The highest proportion of anaphylactic reactions occurred in the 11 - 20-year age group (42.9%).

Discussion

Snakebites are common in KwaZulu-Natal. A study at a similar hospital in this region reported 282 severe bites over a 32-month period.[1] As with similar studies in the region, the highest seasonal incidence was during the warm summer months.[1,2]

The EMU guidelines are based on those of Blaylock.[8] These follow a syndromic approach, which classifies the clinical presentation of the patient, the severity of the bite and appropriate treatment, including antivenom. This approach negates the need to identify the species of snake, focuses on managing the presenting signs and symptoms, and is very effective for early and appropriate management of snakebites. Despite the high number of patients who were admitted to the EMU, most did not have severe complications (81%). However, 46 (19%) developed severe complications that required intensive monitoring and treatment. There was no mortality during the study period using these guidelines.

Most patients who develop severe complications need some form of active medical intervention. The most common complication from snakebites was haemotoxicity (59%), usually involving a thrombocytopenia which, when significant (defined as platelets $<50\times10^9$/l), required antivenom administration. The mechanism of acute thrombocytopenia is not fully understood, but antivenom reverses the effect rapidly and is preferred to platelet replacement. Rapid progressive swelling (RPS) was seen in 39% of patients with complications. The incidence of clinical compartment syndrome in snakebites is low (9% in the selected patient population with RPS), probably as most snake fangs penetrate the subcutaneous tissue rather than the muscle fascial compartment. However, RPS should be monitored closely as it can potentially cause significant morbidity. One of our patients required a fasciotomy and 3 needed limb amputations.

The use of antibiotics in RPS with blistering/bullae is not recommended in the acute setting. The snake's mouth and bite have very few micro-organisms, and venom has antibacterial properties.[1] When infection occurs, the organisms responsible are usually Gram-negative enterobacteriaceae. Gas gangrene and tetanus have not been described in southern African snakebite research.

Children appear to be most vulnerable to snakebites. In our study, the highest incidence of snakebite was in the <20 years age group. Children's natural curiosity and the fact that young boys are used as herders in rural farming areas have been cited as a further risk for snakebites.[6] There is also evidence that children are at higher risk for severe symptoms such as swelling, compartment syndrome and neurotoxic respiratory compromise; Blaylock suggests the high venom/body mass ratio as one of the main causes for this,[1] which implies that the dose of venom in children is relatively larger than adults, making them more susceptible to life-threatening swelling or neurotoxicity. In our study, children <10 years required antivenom more than any other age group. Furthermore, children appear to be at higher risk for allergic reactions and anaphylaxis from the antivenom, as confirmed by our results with the highest incidence (60%) of antivenom-associated complications occurring in children <11 years old. The reasons for this are unclear, but a contributory factor may be that the same dose is given to adults as children.

Antivenom administration is the cornerstone of treating severe life- or limb-threatening snakebites. The dose administered is related to the type of snakebite and the amount of venom injected, and not the weight of the patient. This means that the dose should not be reduced in children. Antivenom was administered to 22 patients (9%), the most common indication being RPS (47%). The mean time to

Table I. Reactions to antivenom administration according to age group

	0 - 10 yrs (*N*=8)	11 - 20 yrs (*N*=7)	>20 yrs (*N*=7)
No adverse reaction	2 (25.0%)	4 (57.1%)	6 (85.7%)
Allergic reaction	3 (37.5%)	0	1 (14.3%)
Anaphylactic reaction	3 (37.5%)	3 (42.9%)	0

antivenom administration from the time of the bite was 16 hours. The initial dose used in this study was 40 ml polyvalent antivenom, with further doses required when patient response was inadequate (e.g. progression of swelling) and when no allergic or anaphylactic reactions were observed. Neurotoxic bites generally require higher doses of antivenom (up to 100 ml). The ideal method of antivenom administration is not clearly established, but guidelines are set in the SAIMR package insert. The effectiveness of antihistamines, hydrocortisone and adrenaline in preventing anaphylaxis prior to antivenom administration has little evidence other than a theoretical basis. The risk of acute allergic reactions and anaphylaxis is not dose-related. Furthermore, the rate of antivenom administration over 10 minutes is recommended by the manufacturer, with no evidence that a slower rate of administration is safer.[1,5]

The relatively high risk of allergic and anaphylactic reactions to polyvalent antivenoms has led to recommendations that it be administered in a hospital setting and not 'in the field'. Some First-World countries have developed more purified antivenoms such as the antivenin (Crotalidae) polyvalent (ACP) and the Crotalidae polyvalent immune fab (CroFab; FabAV) which are effective, with reduced adverse reactions.[7,9] The decision to use antivenom should not be taken lightly, and clinicians must weigh up risks versus benefits. An understanding of the characteristics of both the venom and the antivenom is paramount. Snake venom can cause reversible (e.g. coagulopathies, such as thrombocytopenia) and irreversible (e.g. severe swelling with necrosis and tissue death) injuries. Antivenom used timeously can prevent the progression of injuries from becoming severe or life-threatening, and can be life-saving in cases of neurotoxicity in acute settings. On the other hand are the potential adverse effects of the antivenom. In all cases where antivenom is to be administered, the attending clinician should have full resuscitation equipment and drugs on hand to manage anaphylaxis.

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CHAPTER 3

Estimating the burden of snakebite on public hospitals in KwaZulu-Natal, South Africa

WILDERNESS & ENVIRONMENTAL MEDICINE, **27,** 53–61 (2016)

ORIGINAL RESEARCH

Estimating the Burden of Snakebite on Public Hospitals in KwaZulu Natal, South Africa

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From the Nelson Mandela School of Clinical Medicine (Drs Wood and Hift) and the School of Public Health (Dr Sartorius), University of KwaZulu Natal; and the Ngwelezane Hospital (Dr Wood), KwaZulu Natal, South Africa.

Objective.—We propose a formula as a means to estimate the number and incidence of snakebites treated per annum in KwaZulu Natal (KZN), South Africa.

Methods.—Using an unvalidated formula that includes an antivenom ratio, we crudely estimated the total number of snakebite presentations in KZN. Using antivenom supply data from the central pharmacy, we stratified a sample of 6 hospitals that were surveyed to establish an antivenom ratio, that is, the total number of patients receiving antivenom to the total number of snakebite presentations at hospitals. The antivenom ratio and the average number of antivenom vials for treated snakebites were incorporated into a formula to crudely estimate the number of snakebite presentations. This was then applied to all public hospitals and districts in the region.

Results.—Seventy-eight percent of public hospitals were included. The mean antivenom ratio derived from the sample hospitals indicated that 12% (95% CI, 10–14%) of snakebite presentations received antivenom. We estimated an annual total of 1680 (95% CI, 1193–2357) snakebite presentations to hospitals. Two thirds of cases (1109 of 1680) were in the low-lying subtropical coastal region. Few cases were in the higher, cooler regions of KZN (87 of 1680) or the metropolitan city of Durban (93 of 1680). The overall incidence for KZN was 16/100,000. The estimated cost of snakebite in KZN was between $1,156,930 and $2,827,848.

Conclusions.—We propose an alternative method to estimate the annual number of snakebite presentations to hospitals.

Key words: snakebite, antivenom, antivenom ratio, incidence, mortality, South Africa, KwaZulu Natal, distribution, costs

Introduction

Snakebite is an important disease that is difficult to quantify in terms of patient numbers and outcomes. The worldwide data on snakebite are limited, and region-specific data on snakebite numbers in Southern Africa are lacking. These data are critical to understand disease burden and to institute appropriate prevention and treatment strategies. Global information is sourced from various government departments and global organizations such as the World Bank, World Health Organization, and the United Nations. These reports are supported by scattered studies from hospital records and local surveys in communities affected by snakebite.[1] The current published data suggest that the greatest burden rests in Asia (approximately 15,400–57,600 deaths per annum) and sub-Saharan Africa (approximately 3500–32,100 deaths per annum).[2] Estimates put the number of snakebites in sub-Saharan Africa at 100,000 to 500,000 per year.[3] It is striking that the quoted snakebite numbers have a wide range and fall short of providing specific regions with accurate estimates. This is largely because of poor documentation of snakebites by healthcare practitioners and health facilities, lack of collation of cases by central health authorities, and healthcare practitioners such as traditional healers who have no formal documentation process.[1,4] Snakebite is not a reportable disease, and as a result there is a noticeable paucity of good data from South Africa. In addition, there are no national standardized snakebite treatment guidelines, resulting in different prescribing habits from clinicians in the hospitals of South Africa.

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One region in South Africa known to have a high number of snakebites is KwaZulu Natal (KZN).[5–7] However, there are no accurate data on patient numbers and snakebite distribution. Various authors have noted that the mix of poverty, tropical climates, and a rural subsistence population creates a hotspot for snakebites.[8–10] KZN has areas that have these 3 ingredients. We aim to use a different approach for estimating the number and incidence of snakebites presenting to public hospitals in KZN by using a formula. By combining antivenom supply figures in the province and extrapolating the data derived from the formula, we hope to quantify the distribution of snakebite presentations and the costs to healthcare in KZN.

Methods

SETTING

Serving the health needs of KZN's 10.8 million people are 11 districts with 72 public hospitals. Public hospitals are nonprivate institutions that are free-access hospitals serving the vast majority of South Africans. The majority of these are local district hospitals, 12 are regional hospitals, and 4 are tertiary referral centers.[11–13] The starting point for estimating snakebite numbers is the KZN Department of Health central pharmacy antivenom supply data, based in Durban. The KZN central pharmacy is the only supplier of antivenom to public hospitals in KZN and keeps accurate records. All public hospitals that require antivenom are supplied according to need without constraints. Using these supply figures for a 2-year period, we identified the hospitals that treated snakebites.

SAMPLE POPULATION

Patients who presented to a public hospital in KZN with snakebite were included in the study. Within this group, all patients who were treated with antivenom were admitted for a period of observation. A stratified sample of 6 hospitals spread across the province were selected on the basis of having treated a reasonable number of snakebites with antivenom (Figure 1). Such a selection was made by including those hospitals that prescribed at least 40 antivenom vials during a 2-year period. We made the assumption that these sites had treated enough snakebites to provide an adequate patient sample size for analysis. Unpublished data from a retrospective analysis of snakebite for 5 years at the sixth hospital (a snakebite referral center) in the northeast of KZN were also included. Patient demographic details were stored on a password-protected Excel (Microsoft Corp, Redmond, WA) spreadsheet and anonymously analyzed using a simple numbering system.

DATA COLLECTION AND MEASUREMENT

We collected data on the number of antivenom vials distributed to hospitals in KZN using supply records from the provincial central pharmacy, which is the sole supplier to public hospitals. In addition, a survey using hospital admission records was conducted at each sample site. Any person bitten by a snake who presented to the hospital was entered into the admissions book. Details on whether the patient was envenomated or not were not captured. Those patients who received antivenom were documented. Because not all snakebites presenting at a given facility require antivenom treatment, we crudely estimated the number of snakebites using a formula created by the authors that has not been validated previously. The formula includes the antivenom ratio, which is the proportion of patients receiving antivenom to the total number of patients presenting with snakebite at each sample facility. The formula was then applied to all hospitals that were not in our sample and extrapolated to each district. The total number of snakebite presentations to public hospitals can be calculated using this formula:

$$TS = (V/a)/R$$

where TS is the total snakebite number, V is the total antivenom vials used in a year, a is the average number of vials per patient receiving antivenom treatment, and R is the the ratio or proportion of patients receiving antivenom to the total number of patients with snakebite (antivenom ratio). The term V/a equates to the number of patients treated with antivenom.

DATA ANALYSIS

We used the data from the sample hospitals to calculate the weighted average (scaled by caseload) of the pooled effect size for the average number of vials used per patient as well as the antivenom ratio. We also used the 95% CIs from these estimates to obtain worst versus best case projections of snakebites. The formula, derived from the 6 sample hospitals, was applied to all hospitals treating snakebite to estimate the total number and distribution of snakebite presentations in KZN. Population statistics were retrieved from the KZN Provincial Census data, and hospital admission figures were obtained from the KZN provincial District Health Information Systems database.[11–13] Population for 2013 is estimated using a growth rate of 1.018% applied annually. Ethics approval was obtained from the Biomedical Research Ethics Committee of the University of

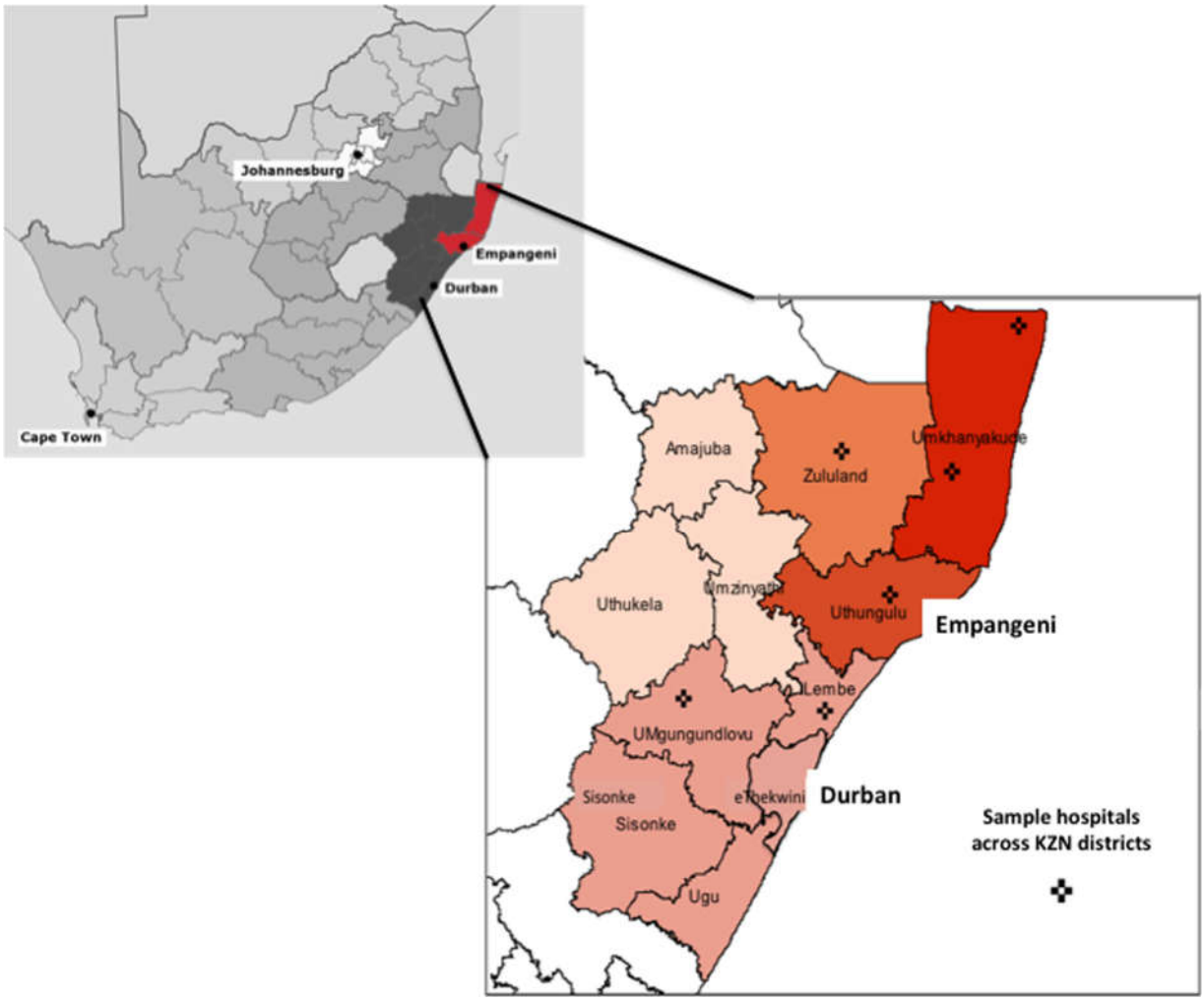

Figure 1. Map of KwaZulu Natal (KZN) province in the context of South Africa and expanded to show the distribution of the 6 sampled hospitals per district.

KwaZulu Natal (Ref. BE 034/01). Informed consent from patients was not obtained because all patient data were analyzed anonymously and numbered (patient names and file numbers were excluded) sequentially. Permission for accessing case files was obtained from the KwaZulu Natal Department of Health. All data were collated using Excel (Microsoft 2010; version 14.4.7) and analyzed using Stata (version 13; StataCorp LP, College Station, TX) in consultation with a statistician. Risk maps were constructed using MapInfo Professional (Pitney Bowes Software, Stamford, CT).

Results

The KZN central pharmacy supplied antivenom to 56 hospitals (78% of all public hospitals) during 2012 and 2013. The number of SAIMR polyvalent antivenom vials (South African Vaccine Producers, Johannesburg, South Africa) that were distributed to these institutions during 2012 and 2013 was 1680. The annual average number of vials used in KZN during this period was 840.

ANTIVENOM RATIO (STRATIFIED SAMPLE HOSPITAL DATA)

The average antivenom ratio (number of snakebites treated with antivenom to number of snakebite presentations) calculated from the 6 sample sites was 0.12 (95% CI, 0.10–0.14). The total number of snakebite presentations from this data set is 8 times the number of cases that received antivenom. The average number of vials used per patient receiving antivenom is 4.9 (Table). The annual mean number of snakebite presentations to the sampled hospitals was 72. Figure 2 graphically represents these data (sampled hospitals numbered 1 to 5 and referral hospital numbered 6) with their associated

Table. Results of the survey from the stratified sample hospitals in KwaZulu Natal

Parameter measured	*Hospital 1* *Khanyakude (2013)*	*Hospital 2* *Zululand (2013)*	*Hospital 3* *Gungungdlovu (2013)*	*Hospital 4* *Ilembe (2013)*	*Hospital 5* *Khanyakude (2013)*	*Hospital 6* *uThungulu (2009–2013)*	*Mean (95% CI)*
Snakebite admissions	60	53	59	21	65	176*	72.3
Antivenom cases	12	5	6	3	3	19.2*	9.2
Average vials/patient	4.2	5.6	4	4	5.7	6	4.9 (0.89–5.36)
Antivenom ratio (WE)† (95% CI)	0.20 (0.11–0.32)	0.09 (0.03–0.21)	0.10 (0.04–0.21)	0.14 (0.03–0.36)	0.05 (0.01–0.13)	0.11 (0.00–0.13)	0.12 (0.10–0.14)
Snakebite deaths during study period	0	1	0	0	1	3	…
Municipal population‡	156,736	186,502	618,563	369,265	71,925	408,795	…
Hospital incidence/100,000	38	28	9.5	5.7	90	48	35.0

* Total number averaged for 5 years.

† Antivenom ratio derived from weighted estimates (WE) for the patients receiving antivenom to the total number of snakebite presentations. The larger the number of patients per hospital, the greater the allocated weighting. The antivenom ratio can be reflected as a percentage by multiplying by 100.

‡ Local municipalities from which patients attend the sample hospitals.11–13

weighting and calculated weighting estimates for the antivenom ratio.

NUMBER AND DISTRIBUTION OF SNAKEBITES IN KWAZULU NATAL USING THE ANTIVENOM RATIO

All hospitals (56 in total) that treated snakebites with antivenom had the formula applied to their data, and the results were extrapolated to each district (for distribution) and KZN as a whole. The estimated total number of snakebite (treated and untreated) admissions per annum in KZN is 1680 (95% CI, 1193–2357). The projected number of snakebite patients treated with antivenom in KZN is 202 (12% of snakebite presentations). The majority of projected case presentations were in the subtropical northeast coast of KZN (Figure 3, region 4) and accounted for 67% (1109 of 1680) of all hospital presentations. As expected, this region treated the greatest number of cases with antivenom (133). Of note was the densely populated Durban metropolitan area, which treated only 93 cases (Figure 3, region 1). The higher, cooler inland areas of region 2 saw very few cases and collectively represented only 5% (87 of 1680) of the total.

ESTIMATION OF THE DISTRICT AND PROVINCIAL SNAKEBITE INCIDENCE

The sample hospitals had an incidence that ranged from 5.7 to 90 per 100,000 population (Table).[11–13] The calculated and extrapolated overall KZN provincial incidence was 16/100,000 population (Figure 4). Two districts in region 4 (uMkhanyakude and uThungulu) had a high incidence, 82/100,000 and 47/100,000 population, respectively. Figure 4 depicts the relative incidences per district in KZN, highlighting the high incidence of snakebite in the low-lying, humid coastal regions compared with the low incidences in the higher, drier inland regions.

COST OF ANTIVENOM TREATMENT IN SNAKEBITE

The cost per vial of polyvalent antivenom (data from KZN central pharmacy) in the public sector is approximately $80. The total cost per annum for an average of 840 vials used equals $67,200. The antivenom cost per patient receiving antivenom (average, 5 vials) is $400. The total cost to KZN for snakebite admissions can be estimated using published data on trauma admissions for which a daily fee has been estimated at an average cost of $243 per patient per day (KZN Department of Health, cost for a ward bed in 2014; unpublished data). In KZN,

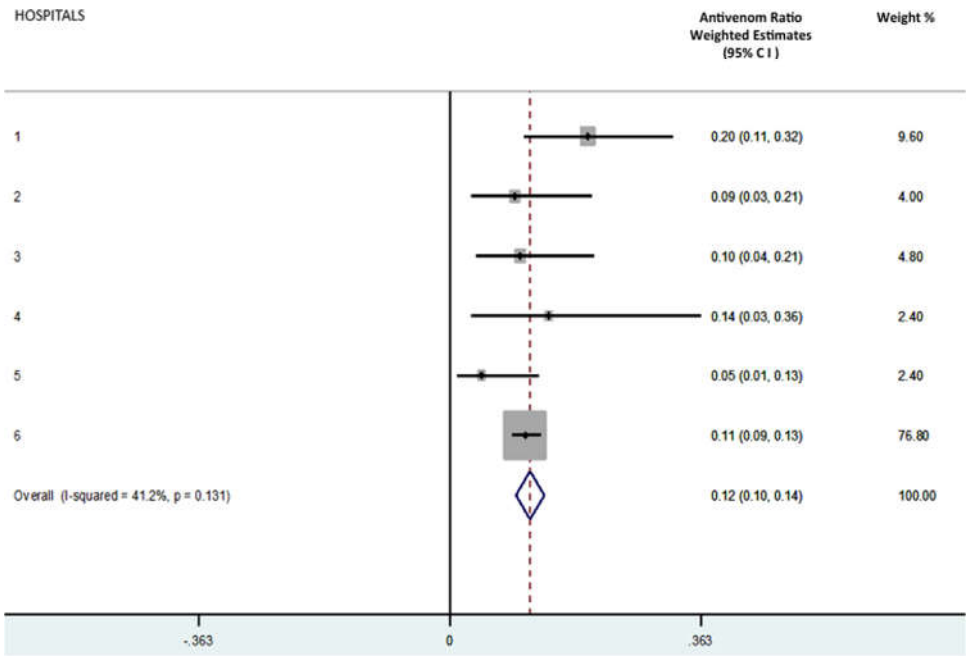

Figure 2. The weighted estimates of each hospital's antivenom ratio (hospitals 1 to 6) plus the overall ratio for the stratified sample.

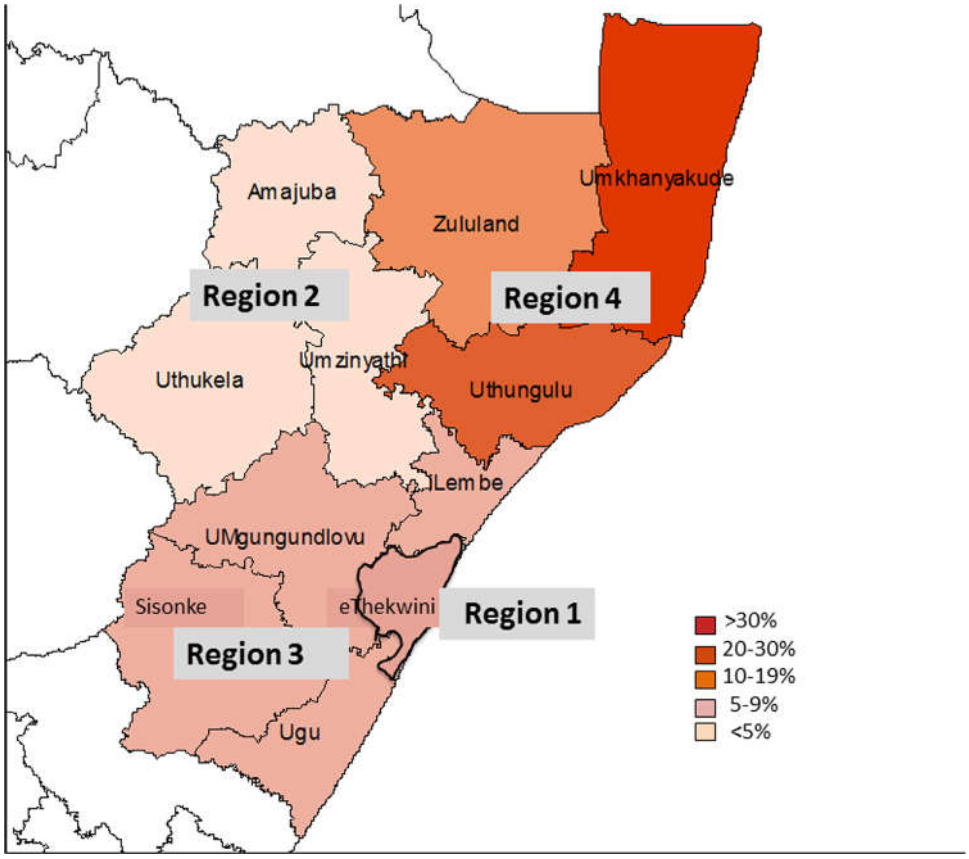

Figure 3. The percentage of snakebite presentations to public hospitals per district in KwaZulu Natal extrapolated from the derived formula.

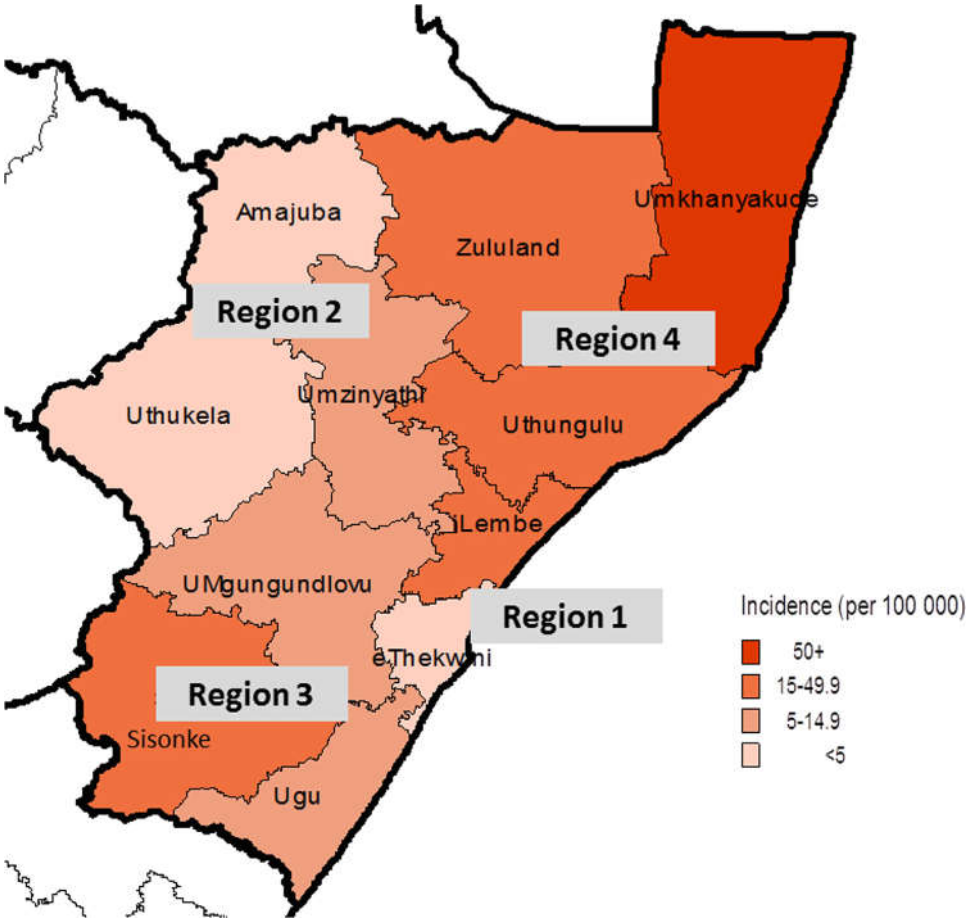

Figure 4. The relative incidence of snakebite presentations to public hospitals per district in KwaZulu Natal.

snakebite is classified under trauma because it is regarded as an injury. Currently, specific costs for admitted snakebite patients have not been quantified in our setting, and the use of trauma figures acts as a crude surrogate for an estimate. Patients who are hospitalized with snakebite spend on average 3 to 7.6 days in the hospital before being discharged.[14,15] Using these values (range, 3–7.6 days), a crude estimate of a single snakebite admission ranges from $703 to $1780. The total cost of snakebite admissions in KZN, based on the low and high hospital stay and the estimated 1680 cases, equals a low estimate of $1,156,930 (95% CI, $821,558–$1,623,145) and a high estimate $2,827,848 (95% CI, $2,008,090–$3,967,404). Added to this cost is the total cost of antivenom per year ($67,200).

Discussion

Strategies to obtain data on snakebites in southern Africa presented in the literature are not accurate and poorly describe case numbers within a specific region. Studies that are community-based using household surveys are challenging because these are labor-intensive and it is difficult to cover large areas.[14] Initial community research should begin within the identified hotspots and possibly be extrapolated to the immediate district. The majority of research in hospitals describes envenomations only, although published data on all snakebite presentations is scarce (envenomation plus non-envenomation bites).[1] Snakebite in South Africa is not a reportable disease, making accurate record keeping unreliable. In response to these difficulties, we have proposed using a formula that incorporates antivenom distribution data and a formula derived from a sample of hospitals to quantify the number of snakebites presenting to public hospitals in KZN as a whole. The basis of this model relies on the accurate antivenom distribution data from the sole provincial central pharmacy. Almost 80% of hospitals in KZN received antivenom during this period, which provided investigators with good provincial coverage for the framework of the proposed model.

Our survey of sample hospitals produced an average antivenom ratio of 0.12, ie, 12% of snakebite presentations were prescribed antivenom. This ratio is supported by previously published research within the province that on analysis yielded an average ratio of 0.1.[5–7,15] These prescribing ratios are lower than those reported by studies conducted in West and East Africa, which report ratios upward of 0.33.[4] Our data are consistent with reported prescribing habits of clinicians treating snakebites in our region during the past few decades.

One vial of South African Vaccine Producers polyvalent antivenom contains 10 mL of concentrated antibodies to the venoms of 10 dangerous snake species. These include the puff adder (*Bitis arietans*) Gaboon adder (*Bitis gabonica*), cobra species (*Naja nivea, Naja mossambica, Naja melanoleuca, Naja annalifera*), mamba species (*Dendroaspis polylepis, Dendroaspis augusticeps, Dendroaspis jamasoni*), and the rinkhals (*Haematochus haematochus*). Our local guidelines suggest an initial loading dose of 5 vials polyvalent antivenom followed by further doses according to clinical response.[16,17] Dosing is stopped when an adequate response is seen, such as cessation of swelling progression, reversal of muscle weakness, or bleeding that has stopped. Patients are further monitored for 48 hours after antivenom treatment. The average number of vials per patient receiving antivenom in this study was approximately 5, which is lower than expected, and in our experience 10 or more vials are usually required to neutralize the effects of envenomation. The significant risk of antivenom anaphylaxis (range, 19%–39%) reported from some studies in the region may explain this trend, causing doctors to stop antivenom infusions before they have been completed.[3,5,7,15]

Our results show that there is significant variation of snakebite numbers across KZN. The subtropical low-lying northeast of KZN accounted for the majority of snakebites, in keeping with other studies showing hot, humid climates in low-lying rural areas to be hotspots for snakebite.[9] The 3 districts representing this region (uMkhayakude, Zululand, and uThungulu) are all underdeveloped and have primarily rural subsistence populations. These observations are further supported by snake distribution data presented by Bates et al,[18] which supports the presence of a numerous varieties of venomous snake species (eg, puff adder and Mozambique spitting cobra) in the eastern coastal region of KZN. Very few snakebites occur in the cooler, higher altitude regions of the north and northwest of KZN, which border on the Drakensberg mountain range, suggesting that altitude and temperature are significant factors in snakebite incidence. Geographical variations within a region clearly affect the number of snakebites. Global estimates and health organization statistics do not bear relevance to this and are often not practical for planning management strategies at the regional and district levels.

Using global studies, Kasturiratne et al[1] estimated the incidence for southern sub-Saharan Africa to be 8.87/100,000 population. The overall incidence of snakebite presentations to public hospitals in KZN was 16/100,000 population. The subtropical coastal districts in our study had higher incidences (81.6/100,000 population in the uMkhanyakude district). This was expected because earlier studies from these areas alluded to similar figures and range from 31/100,000 population to 97/100,000 population.[5–7,15] The higher Amajuba and uThukela regions and the urban Durban metropolitan area saw few snakebites per population. This supports the observation that snakebite distribution is highly variable in KZN and is rare in the higher, cooler areas and in urban environments.[9]

The overall cost of snakebite admissions is significant. The cost of antivenom is relatively low in comparison with the expense of admitting patients with severe presentations for prolonged periods.

When one considers that many snakebites occur during work activities such as farming, cultivating fields, and transiting to and from work, snakebite can be classified as an occupational disease in these settings. A study in South America by Otero-Patiño[10] in rural communities, where agriculture is the main industry, described 85% to 90% of snakebites to be occupational. Sugar cane farming is a major income generator in KZN, and it requires a labor force to manually cut the raw cane before it is processed. This activity makes cane cutters vulnerable to snake encounters. The loss of income to the industry and individual households from snakebite has yet to be estimated.

The proposed method and formula appears to support previous research on snakebites in KZN and our experience in this region. Such a method should be externally and prospectively validated in future research and could potentially be used to monitor the prescribing habits of doctors and the trends of snakebite presentations in KZN with time.

LIMITATIONS

We stratified sample hospitals from a group of hospitals that received antivenom vials for snakebite treatment on the assumption that hospitals treating snakebite would stock antivenom for severe cases. Our sample hospitals were selected as a stratified convenience sample, which reduces the accuracy of the estimates presented. A more comprehensive sampling strategy would provide a more

accurate representation of the snakebite numbers and prescribing habits. In addition, some hospitals and primary healthcare clinics may have treated patients with snakebite and discharged them home without using antivenom during a 12-month period. We attempted to reduce this bias by using 24 months of antivenom distribution data in an attempt to include as many facilities as possible.

This model underestimates the true number of snakebites because it does not account for snakebite presentations that did not present to a hospital, such as those patients who exclusively attended primary health clinics, visited traditional healers, or received home-based care. In some parts of Africa this number far outweighs hospital admissions and can range from 60 to 80%.[19,20] In our region there are no robust data on the number of snakebite patients who do not seek medical attention from hospitals. One local snakebite community survey yielded 39% of snakebite cases that did not present to the hospital.[14] The sample hospitals for this study did not include private hospitals, which do see a small number of snakebites but do not receive the supply of antivenom from the KZN central pharmacy. Private hospitals individually order antivenom directly on a needs basis and this is difficult to quantify. As a principle, any estimate of snakebite numbers will fall short of the true number. This method is reliant on accurate and reliable data on antivenom distribution and reflects public hospital attendees only. Such a method will not apply to countries where antivenom supply is not as well controlled.

Conclusions

Quantifying the number of snakebite presentations is challenging. We have proposed a formula that uses specific parameters as an alternative method to crudely estimate snakebite numbers. Our results from some of the districts are similar to those of previous observational studies done in these areas. More research is required to validate such a method. Of importance is the need for large community surveys that can reflect the proportion of patients who do not present to hospitals. Combining both these approaches would bring us closer to the true snakebite burden in KZN.

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CHAPTER 4

Snakebite in north-eastern South Africa: clinical characteristics and risks for severity

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RESEARCH

Snakebite in north-eastern South Africa: clinical characteristics and risks for severity

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Objectives: To identify the toxicity profile of snakebites and to assess clinical severity.
Methods: An analysis of all patients admitted to Ngwelezane Hospital's Emergency Department with a diagnosis of snakebite over five years was done. All patients were admitted, assessed and standard haematological and biochemical tests were done. Patients were observed for a minimum of 12 hours' observation.
Results: In total, 879 cases were analysed. Envenomation was identified in over two-thirds of admissions. Cytotoxic snakebites accounted for 98% of envenomations. Only four cases of haemotoxic bleeding and five cases of neurotoxicity were admitted. Abnormal laboratory indices correlated with severity: INR > 1 5 (odds ratio 2.25, CI 1.12–4.53; $p = 0.023$), platelets < 100x109/L (OR 2.35, CI 1.01– 5.49; $p = 0.048$), haemoglobin concentration < 8.0 g/dL (OR 5.68, CI 2.15–15.00; $p < 0.001$) and leucocyte count > 10x109 (OR 3.15, CI 1.89– 5.26, $p < 0.001$). Children and delays to admission correlated to and were predictors of severity.
Conclusion: Two-thirds of patients who present to hospital with snakebite will have symptoms of envenomation, with the overwhelming majority having been bitten by cytotoxic species. Some factors correlate to severity and may be useful for anticipating the patient's clinical course.

Keywords: Snakebite, cytotoxic, neurotoxic, haemotoxic, envenomation, emergency, KwaZulu Natal

Introduction

Snakebite constitutes a serious and neglected public health problem in much of the developing world.[1] Of 3 496 species of snake identified worldwide as of April 2015,[2] approximately 600 are venomous.[3] In South Africa there are some 38 venomous species, of which approximately half pose a significant threat to humans and a potentially fatal bite.[4]

There is extensive variability in snakebite from region to region, dependent on the range of species locally present, and environmental and population factors. Given the variability, however, it is essential that experience is reported with reference to a specific area, the characteristics of the snake species inhabiting the region, and also the specific characteristics of the population of that area.[5]

In terms of global burden of disease, Southeast Asia carries the highest burden, followed by sub-Saharan Africa.[6] The difficulty inherent in establishing reliable and representative data for sub-Saharan Africa has been highlighted in a recent meta-analysis.[7] The highest incidence of snakebite in South Africa is in the rural north-eastern coastal belt of KwaZulu-Natal. Small local studies have suggested an annual incidence of snakebite in north-eastern parts of the province of 28–96.5 per 100 000.[5,8–10] Our own recent studies, extrapolated from antivenom utilisation, suggest an incidence within this range (manuscript currently under review).

The snake species most commonly responsible for serious snakebites in KwaZulu-Natal are the puff adder (*Bitis arietans*), a viperid, and the Mozambican spitting cobra (*Naja mossambica*), an elapid. Both produce potent cytotoxic venom. Other snakes responsible for severe bites include four elapids with neurotoxic venom: the forest cobra (*Naja melanoleuca*), black mamba (*Dendroaspis polylepis*), green mamba (*Dendroaspis angusticeps*) and snouted cobra (*Naja annulifera*); species with cytotoxic venom, the gaboon adder (*Bitis gabonica*) and the rinkhals (*Hemachatus hemachatus*) and a colubrid with haemotoxic venom, the boomslang (*Dispholidus typus*).[4] Deaths due to snakebite appears to be infrequent and the reported mortality from these small studies in South Africa is low (0.08–2.67 per 100 000).[7]

Studies over the past 50 years in KwaZulu-Natal have reported similar results with respect to demographics, seasonal distribution, bite characteristics, antivenom use and mortality,[5,8–11] suggesting that little progress has been made in terms of prevention strategies or treatment practice over the past few decades, and confirming snakebite's status as a neglected disease.[12]

We have previously reported our experience of 243 snakebite admissions over a year period in 2007–2008.[11] We now follow this up with a larger study over a five-year period. The purpose of our study was to identify the presenting features of snakebites, to determine the proportion of envenomation, to assess clinical severity, and to identify possible factors that correlate to severity.

Subjects and methods

Setting

Ngwelezane Hospital is the major referral hospital in the subtropical north-east of KwaZulu-Natal (Figure 1) and serves close to 3 million people. It serves the local population of the

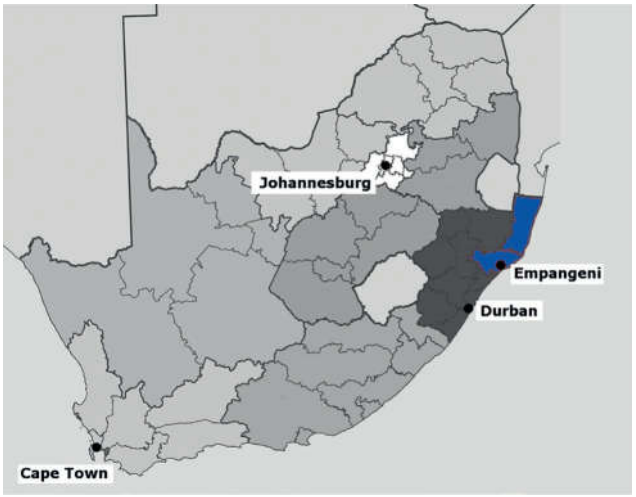


Figure 1: High-incidence snakebite setting in southern Africa. The province of KwaZulu-Natal is shaded in dark grey and abuts on Swaziland and Mozambique in the north. The areas in blue are the Uthungulu (south) and Ukhanyakude (north) administrative districts. These two districts constitute a significant part of the catchment area for Ngwelezane Hospital, situated in the town of Empangeni, are coastal and subtropical in climate, and have a high incidence of snakebite.

uThungulu district and provides regional and tertiary care to 20 district hospitals in the uMkhanyekhude and Zululand districts. The specialist-led Emergency Department (ED) admits all snakebites for a period of observation and workup from the local area and takes referrals for more severe snakebites from district hospitals.

Study sample

Over a five-year period, all patients admitted to Ngwelezane Hospital's Emergency Department with a diagnosis of snakebite were studied. Baseline demographic data were captured on a protected database prospectively and files were retrieved retrospectively from hospital records for more detail such as blood test results and treatment received. Patients whose case files could not be located were excluded from the study. In our local setting patients who are less than 12 years of age are treated as paediatrics cases and are thus grouped as children in this study. Patients were categorised according to clinical presentation. Three categories were identified as Painful Progressive Swelling, ± necrosis (PPS), Bleeding (B) or Progressive Weakness (PW). Patients were further categorised according to severity at presentation: mild, moderate or severe.

Standardised patient care

All patients were treated using a standard institution protocol adapted from the guidelines published by Blaylock[13] (Figure 2). Bites from snakes were confirmed by identifying the presence of characteristic fang marks. All patients were admitted, assessed and standard haematological and biochemical tests were done. Patients received tetanus prophylaxis and, where indicated, analgesia, fluid therapy, antibiotics, and blood products. All patients were observed for a minimum of 12 hours.

Statistical analysis

All data were collected and entered into EpiData. Analysis was performed using Stata version 13 (StataCorp LP, College Station, TX, USA) and MedCalc version 15.4 (MedCalc Software bvba, Ostend, Belgium). Significant differences in categorical data were assessed using standard Pearson chi-square or Fisher's exact test. Ordinal data were compared using Student's t-test or, for non-parametric parameters, the Mann–Whitney U-test. Correlations were analysed using Spearman rank order correlation. Multivariable logistic regression was used to assess factors associated with severity to adjust for the influence of other risk factors and potential confounders. All confidence intervals (CI) are quoted at the 95% probability level. Abbreviations for relevant statistical data include inter quartile range (IQR) and odds ratios (OR). A p-value of < 0.05 was deemed significant.Ethics approval was granted by the Biomedical Research Ethics Committee of the University of KwaZulu-Natal ref: BE034/14.

Results

Data from 879 case files were analysed. Using cyclical regression modelling, we showed a strong repetitive seasonal cycle with a noticeable peak from December to March (Figure 3). The age distribution is shown in Figure 4. The median age at admission was 18 years (IQR 12–28). Although the distribution was essentially similar for both males (447/879) and females (432/879), the median age was slightly higher in females (20 years, CI 18–21) versus males (17 years, CI 17–19) ($p = 0.0009$). We documented 222/879 admissions for children aged less than 12 years, representing a quarter of all admissions.

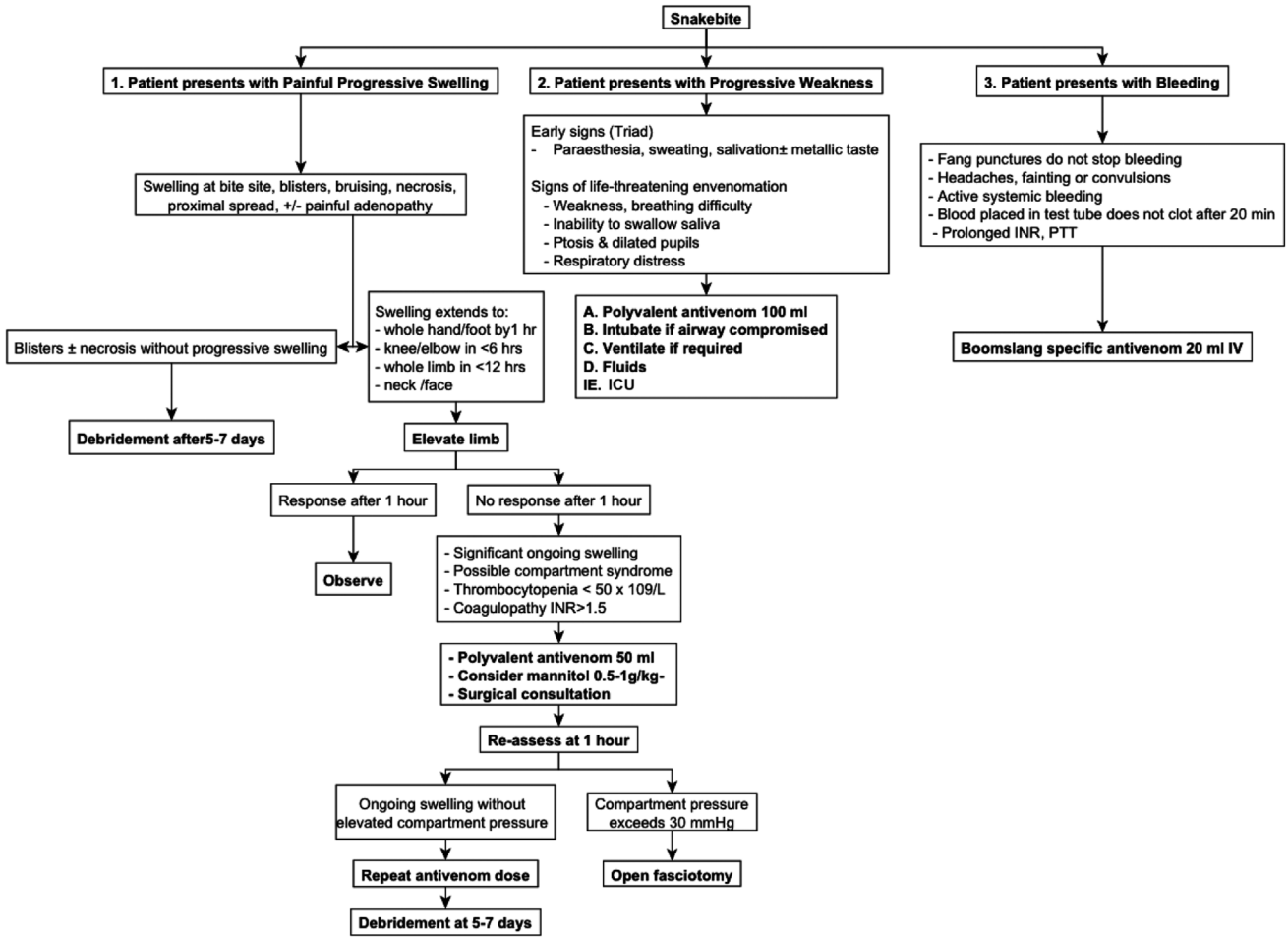
Clinical features

Envenomation was identified in about two-thirds of admissions (534/879); 74% (164/222) for patients younger than 12 years versus 57% (370/657) of patients older than 12 years (odds ratio 2.19, CI 1.57–3.07, $p < 0.001$). The number of dry bites (no envenomation syndrome evident) was high (Figure 5). There was a statistically significant decreasing trend in the risk of envenomation from the first through to the third decade. Isolated signs of bleeding (haemotoxic envenomation) and muscle weakness (neurotoxic envenomation) accounted for only 4 and 5 of the 879 patients respectively, while 98% (525/534) of envenomed patients presented with the syndrome of painful progressive swelling (PPS) following a cytotoxic bite. Three patients presented with painful inflamed eyes following ocular exposure to the venom of a spitting cobra.

In order to study possible predictors of severity, we defined a subset of the patients with PPS as severe if they met the criteria for antivenom administration (see Figure 2) or required surgery. Some 16% (137/879) of patients met the criteria for severe PPS, while the remainder of severe presentations were due to neurotoxicity (5/879) and haemotoxicity (4/879). The remainder of the envenomed patients had lesser degrees of severity (388/879 or 44%) and were classified as moderate. Patients with no local effects from the bite or a minimal inflammatory reaction and pain confined to the bite itself (345/879 or 39%) were classified as mild and termed as dry bite. In all, 45% of (73/164) children with envenomation were classified as severe, compared with 20% (73/370) in adults (odds ratio 3.26, CI 2.19–4.87, $p < 0.001$).

Laboratory values

Median INR was 1.08 (IQR 1.01–1.18). Of these, 57 (8 2%) were above 1.5. Haemoglobin was essentially normal, with a median value of 12.4 g/dL (IQR 11.1–13.5). Leucocytosis was common. The median WCC count was 9.0 x 10^9/L (n = 749, IQR 6.8–12.0); 217 had values greater than 11x10^9/l. The median urea of 3.4 mmol/L (n = 664, IQR 2.6–4.2). Only 16 subjects showed a urea greater than 7.1 mmol/L. The median creatinine concentration was 63 µmol/L (n = 652, IQR 47–78); 22 patients had a value exceeding 115 umol/L (3.4%). No patient in this study required dialysis.



Source: Adapted from Blaylock.[13]

Figure 2: Treatment algorithm for management of snakebite in northern KwaZulu-Natal.

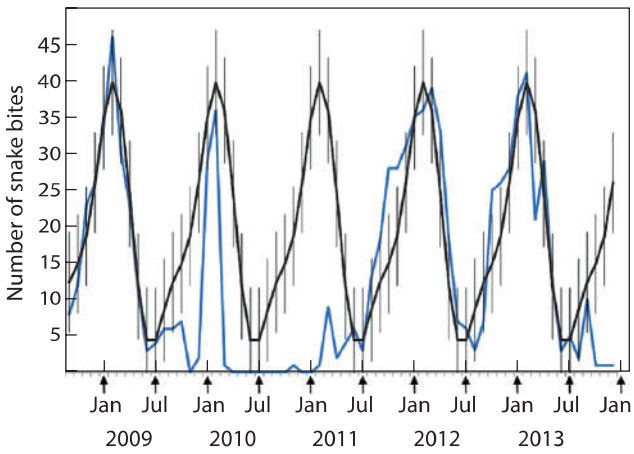


Figure 3: Seasonal distribution of snakebite incidence from September 2008 to December 2013 using cyclical regression. The incidence peaks in January (midsummer) and has a trough in July (midwinter).

Abnormal laboratory indices correlated significantly with severity: INR > 1.5 (odds ratio 2.25, CI 1.12–4.53; p = 0.023), platelets < 100x10^9/L (OR 2.35, CI 1.01–5.49; p = 0.048), haemoglobin concentration < 8.0 g/dL (OR 5.68, CI 2.15– 15.00; p < 0.001) and leucocyte count > 10x10^9 (OR 3.15, CI 1.89– 5.26, p < 0.001). However, their value as accurate predictors for severity is limited by poor sensitivity and specificity. ROC curves are shown in Figure 6. The most predictive laboratory index for severity was the INR; the ROC curve analysis returned an AUC of 0.75 (CI 0 70–0.79).

Delayed presentation from bite

Information on the time from bite to admission was available in 743/879 cases. The median time was 5 hours (IQR 3–10 hours). A delay in presentation was significantly associated with increasing severity. The median elapsed time of the patients with moderate acuity was 5 hours (IQR 3.8–10 hours), and for patients with severe acuity 10 hours (IQR 7–16.8 hours, p < 0.0001).

Referred patients

Most patients were residents of the immediate area (782/879) and only 11% (89/879) had been transferred from outlying district hospitals. Patients transferred from district hospitals to the Emergency Department had a significantly longer delay before presentation than local admissions; a median time of 14 hours (IQR 8–20 hours) versus 5 hours (IQR 8–20 hours, p < 0.001). Patients who were referred with envenomation from outlying hospitals for snakebite were 15 times more likely to be severe than admissions from the local area, 74% (78/106) versus 16% (68/427) respectively (OR 14.7, CI 8.89–24 30, p < 0.001) and 11 times more likely to require antivenom (OR 10.84, CI 6.56–17.89, p < 0.001). Logistic regression suggested that in both cases the elapsed time was redundant when the referral variable was included.

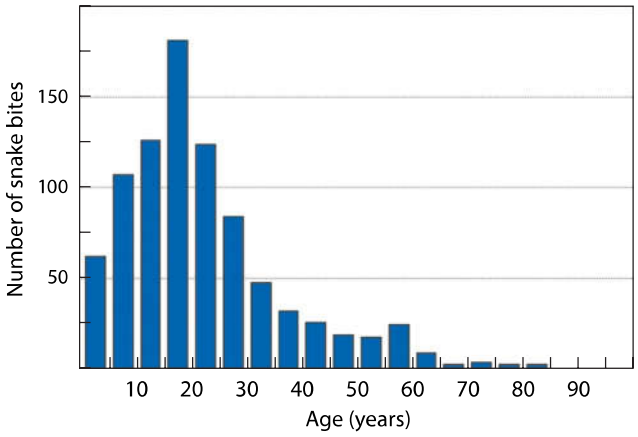


Figure 4: Age distribution of subjects presenting with snakebite.

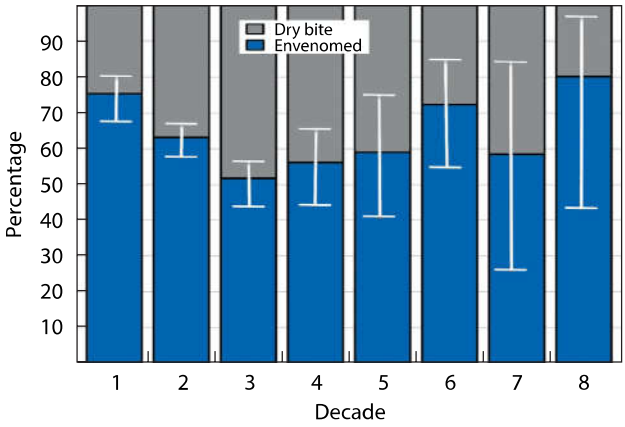


Figure 5: Proportion of cases envenomed per decade of life. Confidence intervals for the proportion are shown by the white bars. The proportion for the second decade is significantly lower than that for the first decade ($p < 0.0001$); the proportion for the third decade is significantly lower than that for the first decade ($p < 0.0001$) and the second decade ($p = 0.002$). No significant differences are shown for the fourth to eighth decades: numbers of subjects are smaller and confidence intervals correspondingly wider.

Management and outcome

Few patients presented with serious systemic toxicity. Fluid and repeated inotrope resuscitation was required in four patients, all of whom had had severe systemic allergic reactions to antivenom. One patient required ventilation. There were no deaths. A total of 96 patients (11.5%) received antivenom. Of these 4.2% (4/96) patients received monovalent antivenom following envenomation by *Dispholidus typus*, a haemotoxic species; the remaining 92 patients received polyvalent antivenom: 5 for neurotoxic envenomation, 87 for severe PPS following cytotoxic envenomation. Children were more likely to require antivenom (45/164 envenomations, 27%) than adults (51/370 envenomations, 14%) (OR 2.37, CI 1.5–3.72; $p < 0.001$). The median dose of antivenom administered per patient was 40 ml (IQR 40–100). Anaphylaxis was documented in 23% (23/96) of patients who received antivenom.

Surgery was performed in 16% (82/525) of patients with PPS; in some patients more than one procedure was performed during their admission. Of these, debridement of the wound with removal of necrotic tissue (76/128 procedures, 59%) and skin grafting (42/128 procedures, 31%) were the most common surgical interventions. Both fasciotomy and amputation were rare in this group: 2% and 6% respectively.

Discussion

Clinical presentation

Snakebites constitute almost 10% of all admissions to the Ngwelezane ED over the high incidence months of December to March. The snakebite incidence in our study for the local district, uThungulu, is 32 per 100 000 population, which is comparable to previous estimates.[5,8–10] This is considerably higher than the incidence of 2.34–3.3 per 100 000 extrapolated for southern sub-Saharan Africa as a whole and exceeds even the value of 12.94–22.61 per 100 000 predicted for eastern sub-Saharan Africa, the area immediately to the north of our province, by a global study.[6]

The age distribution is interesting (see Figure 4). The sex incidence is equal, and the patients young. This pattern does not appear to have changed significantly from earlier series in our area[5,8–11] and in the Kangwane area of far north-east South Africa, which shares a similar climate.[14] The peak risk relative to population distribution is noted in the 10–14 age group, and risk tails off rapidly on either side of this, though females remain at increased risk longer than males, until the age of 24. This pattern contrasts sharply with that seen in both Southeast Asia and South America,[15–19] where it is predominantly young men at risk, bitten in the course of agricultural activities. In our area agricultural activities are not reserved for men, and women are responsible for the tending of agricultural fields and the drawing of water from rivers.

The phenomenon of dry bites from venomous snakes is well described and a third of all admissions in this study showed no signs of an envenomation syndrome. In south Asia rates of envenomation have been estimated at 10–40%,[15] and 23.2% in sub-Saharan Africa.[7] We are, however, surprised to note that the rate of dry bites we observed (39%) was three times that previously reported from our area (13%) in 2004.[8]

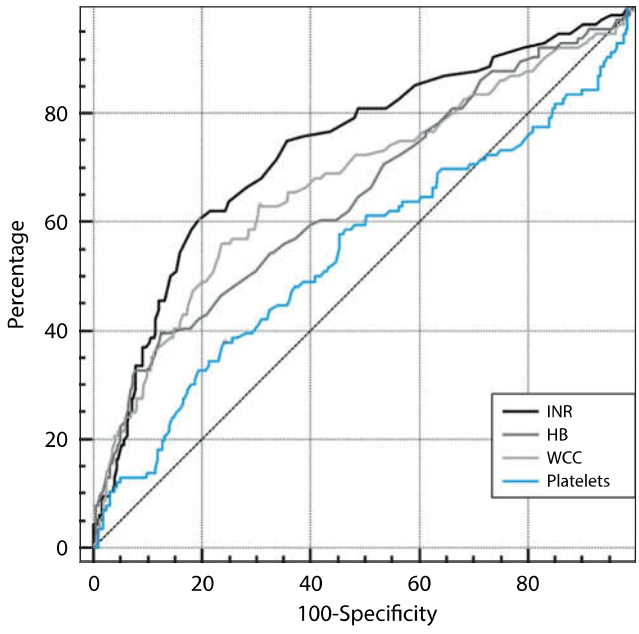


Figure 6: Receiver operating characteristics (ROC) curves: laboratory indices as predictors of categorisation as severe. All indices are poorly predictive; the best performing is INR (AUC: 0.75, CI 0.70–0.79). The Youden index J corresponds to an INR value of 1.18, with a sensitivity of 60.8% and a specificity of 81.2%.

Nearly all our patients exhibited PPS as a consequence of cytotoxic envenomation. We admitted very few patients with evidence of bites from neurotoxic or haemotoxic species. This pattern has not changed from the series in 2004[8] where a ratio of 7 PW:282 PPS was recorded. Indeed, in our environment and contrary to received wisdom, neurotoxic envenomation is rare.[5,8,11] The added rarity of haemotoxic envenomation contrasts with the Asian and North American experience where bites from various viperid and crotaline species commonly cause significant haemotoxicity, often in combination with cytotoxicity.

A striking finding is that serious systemic toxicity is extremely rare in our environment. Very few patients required fluid resuscitation or haemodynamic support, and this was always for allergic reactions to antivenom rather than for the effects of the venom itself. Few of our cases showed elevations in urea and creatinine, renal failure was not a significant factor and no patient required dialysis. Thus acute kidney injury secondary to hypovolaemia or rhabdomyolysis does not appear to be a significant complication of envenomation by southern African snakes in contrast with experience elsewhere, such as India and the Americas, where the incidence of snakebite-related acute renal failure may reach 30%.[20,21]

Laboratory findings

A bleeding tendency and prothrombin time have shown to be predictive of an adverse outcome in India.[22] Our experience suggests that standard laboratory investigations may be helpful in guiding treatment in our population. Several simple abnormal laboratory indices (INR, WCC, platelets and haemoglobin) alluded to a positive correlation with severity; however, their predictive prognostic use could not be supported in this series. Further research on this is required.

Children

Children were nearly twice as likely to be envenomed as adults, and there was a significant decreasing trend in the likelihood of envenomation from the first to the third decade of life. Our clinical experience, though, does suggest that children are particularly vulnerable to snakebite.[11] This may be explained by the greater volume of venom to body size ratio in children compared with adults.[13] We found that children are significantly more likely to have severe presentations and to require antivenom, and almost half of all antivenom we prescribed was for children. The dose of antivenom required to neutralise venom-derived toxins is proportional to the potency and volume of the injected venom, not the bodyweight of the patient. Consequently children require the same volumes of antivenom as adults,[4] with a higher risk of adverse effects. Irrespective of risk, the management of envenomed children is particularly challenging.

Treatment

The treatment protocol we follow would appear to be satisfactory in that we observed zero mortality and only 4.3% of patients required amputation, fasciotomy or skin grafting. The proportion of antivenom prescribed was 11.5% (96/879 patients) with close to a quarter of patients experiencing anaphylaxis. This prescribing rate has remained remarkably constant across several studies in KwaZulu-Natal over the past 23 years, ranging from 9% to12% in 5 studies.[5,9–11]

The majority of cases requiring antivenom administration in our series exhibited severe PPS, accounting for 87 of 96 cases. The protocol we follow, put forward by Blaylock,[13] is essentially based on empirical observation only. A significant proportion of our cases with PPS, 55 of 137, did not require surgery following antivenom administration. This finding supports the thesis that antivenom, when given early, can prevent the progression of swelling and necrosis significantly to the level where surgery may be unnecessary and simple wound care would suffice.

The polyvalent antivenom in use in southern Africa, currently produced by South African Vaccine Producers (Pty) Ltd (SAVP), is a polyvalent partially purified equine-derived antiserum, first introduced in 1928 and active against the venoms of two species,[23] which has been modified at intervals by the addition of further valences, such that it is currently marketed as being active against the venoms of 10 dangerous species. It has, however, not been changed in over 30 years. By modern standards, the degree of purity and specificity is not acceptable, as evidenced by the very high rate of anaphylaxis. The high cost of the added purification processes for antivenom precludes its introduction in many countries. Despite this, all were managed successfully with pre-dose and where required post-dose adrenaline. Only 4 2% manifested a persistent anaphylactic shocked state. This group of patients displayed a circulatory collapse with significant hypotension, loss of peripheral pulses and a depressed level of consciousness. Repeat doses of adrenaline and a fluid bolus immediately after onset of the shock was effective in all but one case, which required an adrenaline infusion and short-term ventilation.

Delays

Delayed presentation and referral from an outlying hospital were strongly correlated with severity. Though this may be due in part to referral bias, with more severely affected cases being preferentially referred, logistic regression analysis suggested a high degree of co-variation for referral and elapsed time since bite. Delays in transfer and in initiating treatment may worsen outcome. Antivenom should be administered as soon as possible to halt the effects of early tissue damage, and a delay in antivenom administration reduces its effectiveness: a recent study in India has confirmed a correlation between a shorter time to presentation and a less severe outcome.[24]

Surgery

PPS is by far the commonest clinical presentation of snakebite in our setting. Patients must be monitored for progression of swelling, compartment syndrome and tissue necrosis. Less than a quarter of patients with PPS require surgery in our setting, resulting in prolonged hospital stays and rehabilitation. The symptoms of cytotoxic subcutaneous tissue damage can mimic an impending intramuscular compartment syndrome and may result in an unnecessary fasciotomy (only 2% in our series).

Envenomation within the muscle groups is very rare: in a series of 42 patients studied by us with ultrasound, we showed that only one had evidence of serious muscle swelling whereas in all other cases the swelling was confined to the subcutaneous tissues (manuscript currently under review), a finding in keeping with another recent study.[25] Current guidelines do not recommend performing a prophylactic fasciotomy merely on the basis of the clinical observation of an alarmingly swollen limb, without direct clinical or invasive evidence of an established compartment syndrome.[15,26–33] It has been shown that North American patients admitted to hospital following crotaline snakebite had a fivefold increased risk of fasciotomy if the primary care was provided by a surgeon rather than a non-surgical clinician.[31] However, limb-saving fasciotomy is indicated when there are sustained high compartment pressures exceeding 30 mmHg and an inadequate response to antivenom.

Limitations

The study is limited in that has been conducted at a single centre. Greater significance and a more reflective extrapolation of results could be achieved in a multi-centre study at sites throughout the province of KZN and even South Africa. The retrospective design for detailed analysis reduces the power and accuracy of the study. A prospective design would be preferable.

Conclusion

We believe that our experience is relevant to much of southern Africa, since many of the species involved are present throughout the region. Certain parameters such as delay to admission and being children are predictive of severity. Outcomes in snakebite have repeatedly been shown to be positively influenced by increased knowledge of snakebite amongst local practitioners.[34,35]

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Declaration – The contributing authors declare no competing interests.

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CHAPTER 5

Classifying snakebite in South Africa: Validating a scoring system

TITLE

Classifying snakebite in South Africa: Validating a scoring system.

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RUNNING TITLE

A severity scoring system for snakebite in north-eastern South Africa.

KEYWORDS

antivenom
fasciotomy
snakebite
surgery

ABBREVIATIONS

ATI	Active treatment indication
AUC	Area under the curve
ROC	Receiver operating characteristics
NPV	Negative predictive value
PPV	Positive predictive value
SS	Severity score
ZSSS	Zululand snakebite severity score

WORD, FIGURE AND TABLE COUNT

Words	2745
Tables	4
Figures	2

ABSTRACT

Aims

The purpose of our study was to develop and validate a severity scoring system to facilitate the management of snakebite in South Africa by allowing early identification of patients at increased risk of a severe course.

Methods

Clinical and laboratory data were prospectively collected on all patients with confirmed snakebite who were admitted to the Ngwelezane Hospital Emergency Department from December 2008 to December 2013. Using the need for an Active Treatment Intervention (ATI), which we defined as meeting the indications for antivenom administration on our standard management algorithm, or the need for a surgical intervention, as a proxy for severity, we analysed our data for factors present on admission which were predictive of an ATI which were then combined into a score. The optimal cut-off score for predicting an ATI was identified by ROC curve analysis. The score was then tested prospectively for accuracy in a new validation cohort consisting of 100 patients admitted for snakebite to the same hospital from 01 December 2014 to 31 March 2015.

Results

146 of 879 snakebite admissions in the development cohort and 40 of 100 in the validation cohort reached the primary end point of an ATI. Six risk predictors for ATI were identified from the development cohort: age <14 years, delay to admission >7 hours, white cell count > $10x10^9$ cells/l, platelet count<92 $x10^9$/l, haemoglobin <7.1 g/dl, INR >1.2. Each risk predictor was assigned a value of 1; ROC curve analysis returned a score of 4 as the optimal cut-off for prediction of an ATI (AUC 0.804; 95% CI 0.758-0.84). Testing of the score on the validation cohort produced a sensitivity of 22.5% and a specificity of 96.6%. The PPV and NPV were 81.8% and 65.2% respectively.

Conclusions

Our scoring system, which we propose to name the Zululand Snakebite Severity Score (ZSSS), is a useful adjunct to clinical assessment in managing snakebite. A patient with a positive result has an 80% probability of progressing to the point where an ATI is indicated. Its value is greatest in those patients who fall in the mild to moderate clinical category. This score now requires validation on a wider scale across South Africa, to determine its accuracy in areas other than those in which it was tested.

INTRODUCTION

There are some 38 venomous species in South Africa, of which approximately half are dangerous to humans [1]. Snake species and density vary across the regions of South Africa [2]. Prevalent species in the north-eastern regions, including the province of KwaZulu-Natal, include the Mozambique spitting cobra (*Naja mossambica*) and puff adder (*Bitis arietans*), an elapid and viperid respectively, both of whom have a potent cytotoxic venom; the black mamba (*Dendroaspis polylepis*) and various cobra (*Naja)* species, all elapids possessing potent neurotoxic venom resulting in progressive muscle weakness; and the boomslang (*Dispholidus typus*) a colubrid with a haemotoxic venom causing potentially fatal bleeding.

The severity of a snakebite is highly variable and dependent on numerous factors. Snakes will utilize their venom differently depending on the situation, controlling the volume injected and the fang contact time with their prey [3]. Defense bites that are designed to fend off danger may in some cases deliver less or no venom, resulting in a dry bite [3-6]. The potency of venom varies with the species of snake and in larger snakes the volume of expelled venom is usually higher [3,6]. In the case of cytotoxic bites, the severity of injury is critically dependent on the body part bitten and the depth at which the venom is injected.

In the absence of objective criteria, the presumed severity of a bite is typically dependent on the attending doctor's own experience and clinical judgment. This process is highly subjective. The severity of envenomation may not be initially appreciated since cytotoxic swelling may progress insidiously, as may the effects of systemic toxicity resulting in shock, and coagulopathy may not be identified until the patient manifests potentially lethal haemorrhage.

Guidelines have been developed to assist doctors to treat patients with snakebite. The recommendations on which our own institution's treatment protocol is based were developed in 2005 and are largely derived from the knowledge and experience of a single surgeon [7]. Most guidelines are based on clinical grading systems that rely on the clinicians' ability to evaluate the clinical manifestations evident in the patient. A number of scoring systems for use in North American crotalid bites have been published: coagulopathy is a major feature of such bites and these systems typically include coagulation studies [8-11]; such systems

are unlikely to be directly transferable to the bites of other snakes with a different toxicity profile. Dart *et al.* [12] proposed a complex guide for crotalid bites in the form of a detailed scoring system, the *snakebite severity score* (SSS). This detailed scoring system is limited by a reliance of subjective judgement by the physician, the time it takes to do the score in the clinical setting and the fact that it was validated retrospectively. Scharman and Noffsinger [13] modified the SSS score for copperhead snakebites by excluding the coagulation abnormality parameter and adding a *progression of swelling* parameter to produce a score based on clinical assessment alone. Gold *et al.* [6] described three parameters to guide clinicians when assessing snakebite in the United States. Two of these parameters are clinical; the third parameter is the presence of coagulation abnormalities. Some authorities find the published scoring systems to have little value in the clinical setting and believe they are of more value in the research setting then in clinical practice [14].

That said, the need for an objective and reliable scoring system persists. Bites from the most venomous South African snakes are often severe and may be fatal; there is thus an imperative to identify the more severe cases early and to treat them vigorously. On the other hand, the mainstay of treatment in South Africa is a polyvalent equine antiserum with a venerable ancestry extending back to 1928. Initially developed as a bivalent antiserum, it is now raised against venom derived from 10 species[15]: its use is associated with a high rate of anaphylaxis and it is essential that its use is restricted to patients who really require it.

We therefore undertook a study to identify those factors most strongly predictive of an adverse outcome in our population, arising from which we propose a scoring system called the Zululand Snakebite Severity Score (ZSSS) that is validated in our setting. We suggest that its greatest value is in identifying those patients who did not appear overtly seriously affected at first presentation, but are at high risk of progression to severity over the ensuing hours. In such cases intensive monitoring and repeated evaluation is mandatory, and the early use of antivenom may be justified.

SUBJECTS AND METHODS

Setting and participants

We studied all snakebite admissions to the Emergency Department at Ngwelezane hospital, a regional referral hospital in the warm, humid and subtropical north-eastern coastal region of the province of KwaZulu-Natal, South Africa, which has a very high incidence of snakebite [15-19]. This region, commonly known as Zululand, the ancestral home of the Zulu people, has a population of approximately 3 million. All patients admitted with a diagnosis of snakebite were included. All patients were treated with a standard protocol based on the recommendations of Blaylock [7].

Outcomes

The primary outcome was an Active Treatment Intervention (ATI), which we defined as the administration of antivenom triggered by the patient's meeting the criteria for this laid down in our institutional protocol, or a surgical procedure at any stage during their admission. Antivenom was administered only in patients who met the agreed criterion and the final decision was made by senior emergency medicine specialist with extensive experience in snakebite. The indications for antivenom treatment were: severe cytotoxic swelling, active bleeding in the case of haemotoxic envenomation, or symptomatic weakness in neurotoxic envenomations. The surgical procedures were defined as debridement of wound necrosis, skin grafts, fasciotomy for compartment syndrome or amputations, and the decision for this was made by a senior surgeon with experience in the management of snakebite.

Study design

We performed a formal validation study using 2 separate patient cohorts. The development cohort consisted of all patients with snakebite who presented to the Ngwelezane Hospital Emergency Department from December 2008 to December 2013. Standard data on these patients had been prospectively collected as part of an ongoing study and data from 983 admissions were retrieved and analysed retrospectively. Factors predictive of ATI were identified using bivariate and multivariable adjusted logistic regression. Receiver operating

characteristic curve analysis was performed and the optimal cut-off score for predicting an ATI identified. These factors were then used to develop a standard scoring system.

The score was then tested prospectively for accuracy in a new validation cohort consisting of all patients admitted for snakebite to our unit from 01 December 2014 to 31 March 2015. In addition, the optimal cut-off score in the validation cohort was determined and compared to the optimal cut-off score in the development cohort. All other factors were unchanged between the two cohorts, including the definitions of ATI, the indications for surgery or antivenom, treatment protocols and the identities of the senior staff supervising therapy.

Ethics approval was granted by the Biomedical Research Ethics Committee of the University of KwaZulu Natal: Reference BE034/14.

Statistical analysis

Data were stored on a protected Excel database (Microsoft 2010; version14.4.7) and were analysed used Stata 13.0 (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP and statistical package 3.0.3 (2015)). Associations between ATI and categorical predictors were assessed using a Pearson χ^2 or Fisher's exact test. Differences in mean of continuous variables were tested using a Student's t-test. For non-parametric data the Wilcoxon rank-sum test was used. A p-value of <0.05 was considered significant. Factors predictive of ATI were identified using bivariate and multivariate analysis and cut-off points determined by ROC curve analysis.

RESULTS

We recorded 983 admissions for snakebite over the period December 2008 to December 2013. Of these 104 were excluded as the clinical records were incomplete. 879 patients were therefore entered into the development cohort. Prospective data for 100 admissions over the period from 01 December 2014 to 31 March 2015 were used for the validation cohort (the round number of 100 is coincidental). Demographic and laboratory data for both cohorts are presented in Table 1. There were significant differences in age, elapsed time from bite, white cell count INR and clinical estimation of severity between the two cohorts.

Development cohort

146 of 879 snakebite admissions reached the primary end point of an ATI. Antivenom alone was administered to 64 patients, 49 of 879 patients received a surgical intervention without antivenom and 33 patients received both. Table 2 shows the ATI risk predictors derived from multivariate analysis. Individually no parameter was strongly predictive for ATI. We therefore combined them using a scoring system in which a positive criterion attracted a score of 1. Further testing revealed that weighting the individual criterion using the coefficients derived from the logistic regression did not provide significantly more accurate prediction than use of the crude score of 1. Similarly, adjusting cut-off values slightly to a more easily-used figure did not significantly decrease the accuracy of the score; e.g. age was adjusted to 12, since this coincides with the age definition for a paediatric patient in our health system. Therefore, in order to promote ease-of-use, we settled on a standard score of 1 per positive criterion and the cut-off values shown in Table 3, to produce a severity score (SS) on a six-point scale. ROC curve analysis returned a value of 4 as the optimal cut-off for prediction of an ATI (AUC 0.789; 95% CI 0.736-0.841).

Validation cohort

40 of 100 patients reach the primary outcome of an ATI. Antivenom alone was administered to 19 patients, 4 patients underwent a surgical intervention without antivenom and 17 patients received both. Within the validation cohort 37 of 100 patients had one or more risk parameters. Applying the SS to this cohort, ROC curve analysis confirmed a cutoff score of 4 as the optimal value for prediction (AUC 0.807; 95% CI 0.728-0.886). The accuracy of the SS in predicting progression to an ATI is summarized in Table 4.

DISCUSSION

Snakebite patients who are obviously severely affected, such as those who present in systemic shock, have active bleeding, manifest neurotoxic muscle weakness or have gross cytotoxic swelling, are easily identified by the admitting doctor and the decision to prescribe antivenom early or plan for surgery is clinically intuitive. However, it is within the mild to moderate envenomation group that a portion of patients will progress to a severe clinical

outcome requiring an ATI. The decision to prescribe antivenom appropriately in these patients is difficult. The risk of anaphylaxis using the South African Vaccine Producers (SAVP) polyvalent antivenom in our region (South African Vaccine Producers, Johannesburg, South Africa) is significant; studies report rates of between 25% and 73% [16,18-20]. Bearing this in mind, doctors must weigh the benefits of antivenom against the risks of anaphylaxis.

Ours is the first attempt to objectively grade snakebites in South Africa. Our scoring system aims to predict which patients will require more aggressive treatment. The ATI group are intuitively those patients who have had a more severe clinical course, and ATI could possibly act as a surrogate marker for severity. The difficulty in grading the severity of the patient by judging the swelling post envenomation is evident when in our experience there is no consistency among doctors who treat snakebites. In our validation cohort 14 of 40 patients who received an ATI were initially assessed as not severe. This supports the view that there is a group of patients that are clinically assessed as non-severe yet progress over time to a more severe course and require an ATI such as antivenom or some form of surgery.

Identifying simple parameters, such as age < 12 years and delay to admission, and noting abnormal admission blood results such as the INR, haemoglobin, white cell count and platelets, the doctor can rapidly score a patient and predict whether they will require ATI. Since the envenomation syndrome is a dynamic process, a guideline that includes a dynamic clinical parameter is ideal and should always be included [14]. In Figure 3 we propose a new guideline that incorporates both clinical assessment and the SS. The SS component will support the doctor's initial clinical assessment in those cases where classifying patients is challenging. Clinicians who score snakebite patients as 4 or more can be reasonably confident that the patient will suffer a more severe clinical course, and will most likely require ATI. If a patient has a positive score, there is an 82% probability that they will progress to an ATI, based on the PPV of the validation cohort. This will alert the doctor to the patient's potential severity and the need to prescribe early antivenom or to plan for surgery. These results support the ZSSS as a "rule in" tool for patients who require ATI.

The lower negative predictive value of the SS does not however guarantee that those patients with a score of less than 4 will not progress to a more severe outcome. This is a limitation

that should be born in mind when using the SS and a period of observation is advocated in these patients. Though the patient with a score below 4 has a 65% probability that they will not progress to an ATI, 35% will indeed do so. Should the score pass into common practice, it is critical that clinicians understand that a low score should not be viewed as reassuring, as one third of these patients will still progress to an ATI. It is essential that all snakebite victims with evidence of a significant bite remain under observation for at least 24 hours.

The risk predictors we identified for ATI and indirectly severity are in keeping with reports from other countries. Although the snake species from Asia and the Americas differ from the South African species, there do appear to be some consistent predictors which include age, coagulation abnormalities, low haemoglobin, leukocytosis, thrombocytopenia and delays in initiating treatment. These factors correlate with adverse outcomes in the Asian and North American viper species [9,11,12,21,22]. It is notable that acute kidney injury is a significant complication of Indian snakebites. One study from Southern India reported acute kidney injury in 28% of snakebite patients with a significant association with mortality [23]. We in contrast found no correlation with severity and in our setting acute kidney injury is seldom reported [16,18,19].

Limitations

We acknowledge the difficulty of clearly defining true severity and the influence that clinical judgment and experience have in influencing a doctor's decision to proceed to an ATI. The potential severity of cytotoxic bites is highly dependent on the site of the bite: significant swelling in the neck may compromise the airway and even restricted swelling in a tight facial compartment may result in a compartment syndrome or serious necrosis, whereas the body may be able to accommodate envenomation in loose tissue more effectively.

The SS will have to be validated for use in other areas of southern Africa with a different spectrum of snake species, and may require modification. In the west and centre of the country for instance, the Cape cobra (*Naja nivea)* and rinkhals (*Hemachatus haemachatus*) are common, whereas the Mozambican spitting cobra, possibly the most frequent source of severe snakebite in our area, and black mamba are not encountered; other species, such as the puff adder are common to both. Until our SS has been validated (or modified) for use

across South Africa, we propose to name it the Zululand Snakebite Severity Score (ZSSS): a true South African Severity Score may follow.

We believe that the species of snake inflicting the bite may in itself be a potent predictor of the likelihood of a severe outcome. Among the cytotoxic species found in our area, the night adder (*Causus rhombeatus*) and southern stiletto snake (*Actractapsis bibronii*) inflict a bite resulting in painful swelling which is almost invariably self-limiting and does not require treatment, and the South African polyvalent antivenom is not active against their venom. Bites from the puff adder and Mozambican spitting cobra by contrast commonly result in severe painful progressive swelling requiring an ATI. Snakebite victims in our region are rarely able to identify the species of the offending snake [19]. There are as yet no immunological-based tests for the identification of specific venom antigens in the blood of southern African snakebite victims, a technique which has proved extremely useful in other settings [24]. Such identification might substantially improve prognostication, and we intend developing such testing.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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TABLE 1

Patient characteristics of the Development (N=879) and Validation cohort (N=100

Characteristic		Development Cohort	Validation Cohort	p
Age: mean (SD)		21.7 (15.0)	15.7 (13.6)	<0.001
Children (<12): n (%)		222 (25.3 %)	57 (57.0 %)	<0.001
Sex	Female Male	431 (49.1 %) 447 (50.9 %)	42 (42.0 %) 58 (58.0 %)	0.179
Elapsed time between bite and admission (hours): mean (SD)		9.5 (17.4)	10.4 (9.6)	0.614
Elapsed time between bite and admission:	<6 hours ≥6 hours	438 (59.0%) 305 (41.0%)	47 (47.0%) 53 (53.0%)	0.023
Urea (mmol/l)		3.4 (2.6-4.2)	3.7 (2.8-4.3)	0.216
Creatinine (mmol/l)		63 (47-78)	57 (36-88)	0.605
White Cell Count ($x10^9$/l)		9 (6.8 -12)	12.6 (9-17)	<0.001
Platelets ($x10^9$/l)		248.5 (196, 320)	271 (204-368)	0.113
Haemoglobin (g/dl)		12.4 (11.1-13.5)	12.6 (11.5-13.7)	0.065
INR		1.08 (1.01-1.18)	1.2 (1.1-1.4)	<0.001
Estimation of severity by admitting doctor	Severe Not severe	146 (16.6%) 733 (83.4%)	26 (26.0%) 74 (74.0%)	0.019

TABLE 2

Multivariable adjusted association between risk factor predictors and Active Treatment Intervention (ATI) cases in Development cohort (N=574*) using logistic regression modeling. C.I. = 95% confidence interval

Calculated ATI risk predictor and optimal value	**AUC**	**Odds (95% CI.)**	**p**	**Percentage of ATI cases in which criterion is positive**
Age < 14 yrs	0.657	2.13 (1.27 – 3.57)	0.004	57%
Duration > 7 hours	0.718	4.63 (2.71 - 7.89)	<0.001	53%
WCC > 10 x 10^9/L	0.69	3.15 (1.88 – 5.26)	0.023	69%
INR > 1.2	0.758	2.25 (1.12 – 4.53)	<0.001	17%
Platelets < 92 x 10^9L	0.508)	2.35 (1.01 – 5.49)	0.048	11%
Haemoglobin < 7.1 g/dL	0.685	5.68 (2.14-15.00)	<0.001	3%

TABLE 3

Zululand Snakebite Severity Score (ZSSS). A score of 4 to 6 is significant for ATI

ATI risk predictors	**Allocated score**
Children < 12 years	1
Duration > 7 hours	1
WCC> 10 x 10^9/l	1
INR > 1.2	1
Platelets < 100 x 10^9/l	1
Haemoglobin < 8 g/dl	1

TABLE 4

Accuracy of 4 or more risk predictors in patients for ATI in both the Development and Validation cohorts. CI = 95%Confidence Interval

	Development Cohort	**Validation Cohort**
Sensitivity	17.8% (10.9 – 26.7)	22.5% (10.1-38.5)
Specificity	98.7% (97.3-99.5)	96.6% (88.5 – 99.6)
Positive Predictive Value (PPV)	75% (57.8-83.4)	81.8% (54.4 – 91.0)
Negative Predictive Value (NPV)	84.9% (76.1-93.9)	65.2% (44.0 – 94.0)

FIGURE LEGENDS

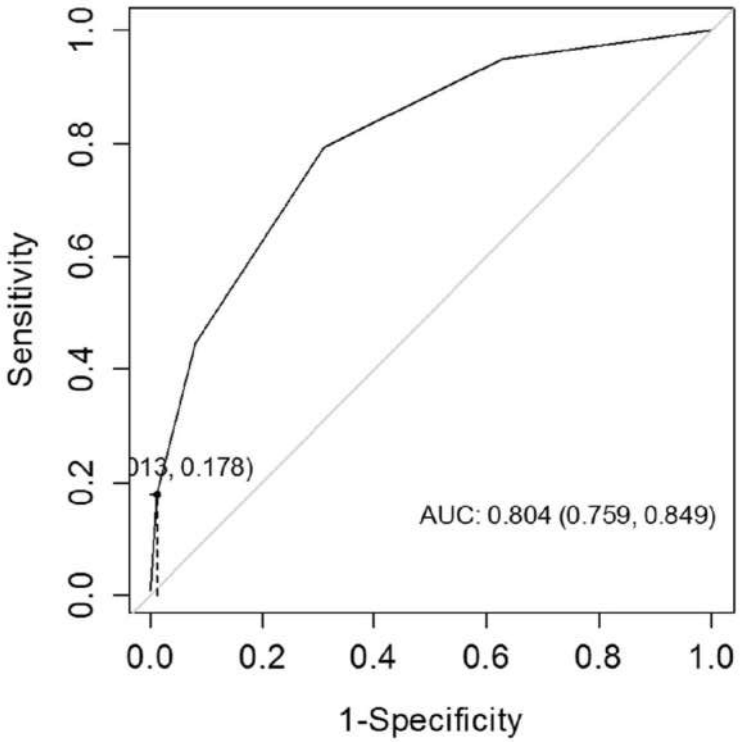
Figure 1

ROC curve analysis of optimal breakpoint for a crude score of > 4 as a predictor for ATI. (A) Development cohort (N=879). (B) Validation cohort (N=100).

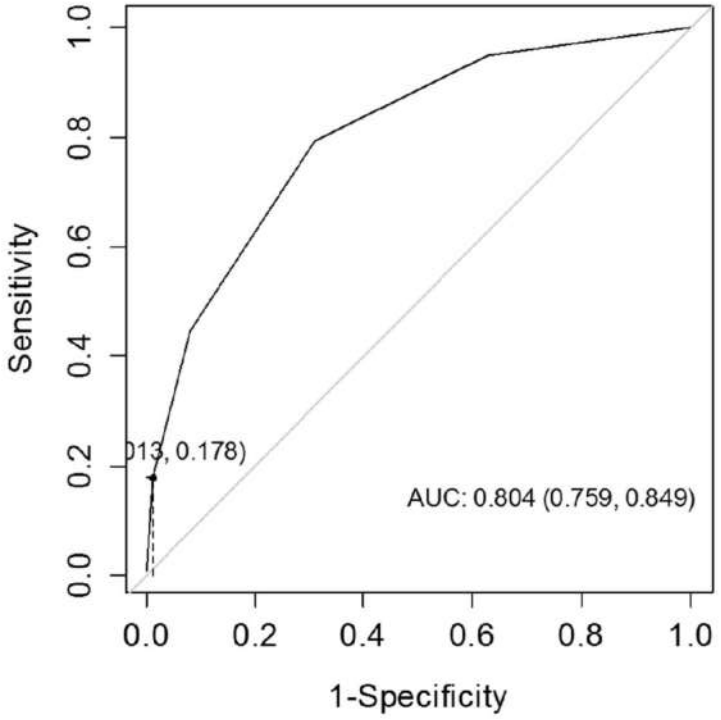
Figure 2

Proposed snakebite management guideline for KwaZulu Natal

FIGURE 1

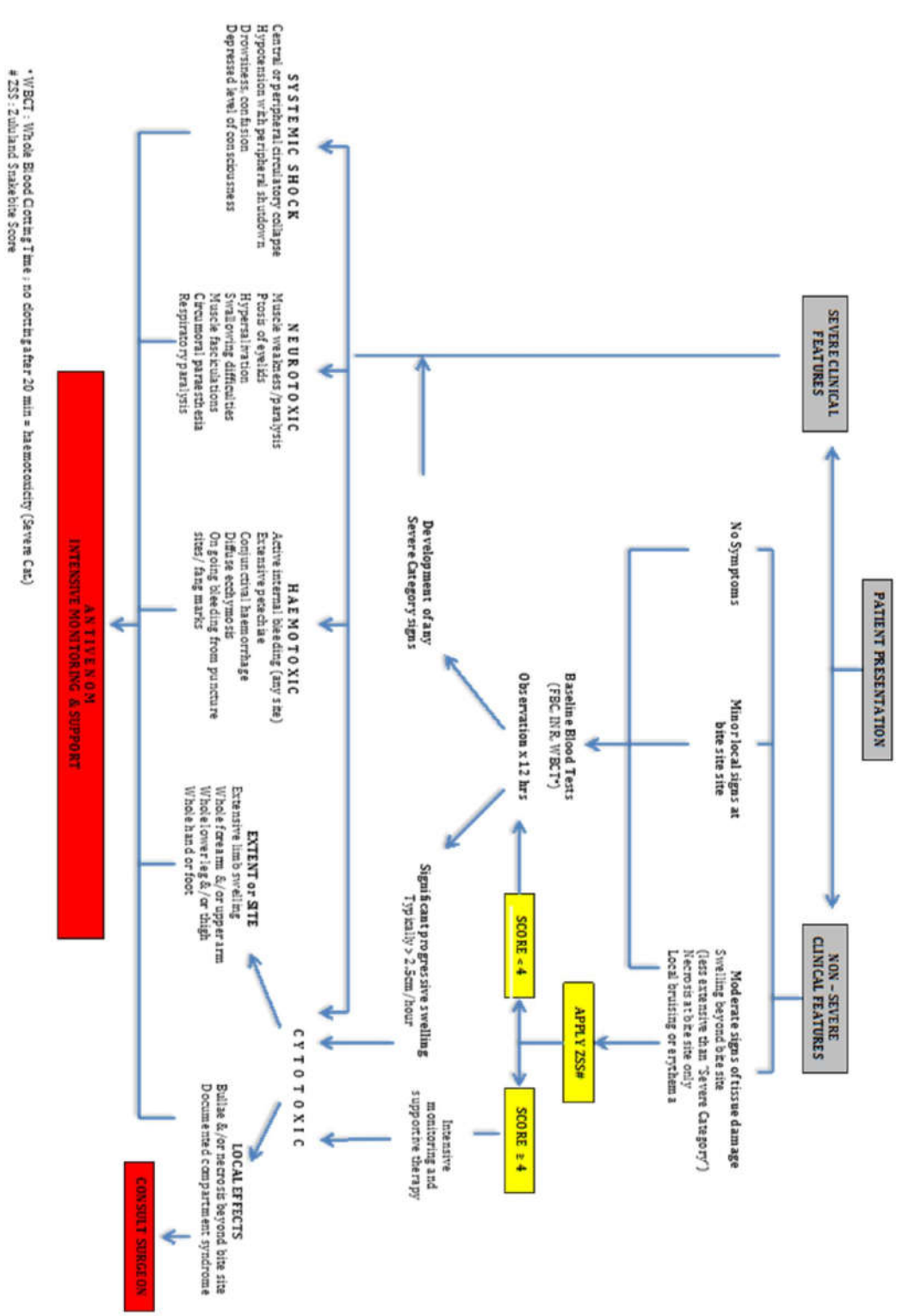

Sensitivity
1-Specificity
0.0
0.2
0.4
0.6
0.8
1.0
013, 0.178)
AUC: 0.804 (0.759, 0.849)

A


Sensitivity
1-Specificity
0.0
0.2
0.4
0.6
0.8
1.0
013, 0.178)
AUC: 0.804 (0.759, 0.849)

B

FIGURE 2


PATIENT PRESENTATION
SEVERE CLINICAL FEATURES
NON - SEVERE CLINICAL FEATURES
No Symptoms
Minor local signs at bite site
Moderate signs of tissue damage
Swelling beyond bite site
(less extensive than 'Severe Category')
Necrosis at bite site only
Local bruising or erythema
Baseline Blood Tests
(FBC INR WBCT*)
Observation x 12 hrs
APPLY ZSS#
SCORE < 4
SCORE ≥ 4
Development of any Severe Category signs
Significant progressive swelling
Typically > 2.5cm/hour
Intensive monitoring and supportive therapy
SYSTEMIC SHOCK
Central or peripheral circulatory collapse
Hypotension with peripheral shutdown
Drowsiness, confusion
Depressed level of consciousness
NEUROTOXIC
Muscle weakness/paralysis
Ptosis of eyelids
Hypersalivation
Swallowing difficulties
Muscle fasciculations
Circumoral paraesthesia
Respiratory paralysis
HAEMOTOXIC
Active internal bleeding (any site)
Extensive petechiae
Conjunctival haemorrhage
Diffuse ecchymosis
Ongoing bleeding from puncture sites/ flag marks
CYTOTOXIC
EXTENT or SITE
Extensive limb swelling
Whole forearm &/or upper arm
Whole lower leg &/or thigh
Whole hand or foot
LOCAL EFFECTS
Bullae &/or necrosis beyond bite site
Documented compartment syndrome
ANTIVENOM
INTENSIVE MONITORING & SUPPORT
CONSULT SURGEON
*WBCT : Whole Blood Clotting Time ; no clotting after 20 min = haemotoxicity (Severe Cat)
ZSS : Zululand Snakebite Score

CHAPTER 6

Ultrasound findings in 42 patients with cytotoxic tissue damage following bites by South African snakes

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Ultrasound findings in 42 patients with cytotoxic tissue damage following bites by South African snakes

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ABSTRACT

Background Snakebites that have cytotoxic venom can cause significant soft tissue swelling. Assessing the site and degree of swelling using ultrasound as a non-invasive technique would be an important tool for instituting appropriate treatment.

Methods Forty-two patients who presented to a referral hospital in South Africa with cytotoxic swelling of the limbs from snakebite were assessed using ultrasound. The envenomed limb of each patient was scanned at the point of maximal swelling and compared with the unaffected limb at the same site. Data were presented as an expansion coefficient defined as the ratio of the thickness of tissue structure (subcutaneous tissue or muscle compartment) in the envenomed limb to that in the unaffected limb. A p value of 0.05 was regarded as significant, and 95% CIs were expressed throughout.

Results The majority of bites were in the upper limb (27/42). Twenty-five patients were children less than 12 years. Tissue expansion was noted in both the subcutaneous and muscle compartments of the envenomed limbs. The site of swelling was predominantly in the subcutaneous tissues, while swelling in muscle compartment was limited (the mean expansion coefficient for subcutaneous tissues was 2.0 (CI 1.7 to 2.3) vs 1.06 (CI 1.0 to 1.1), respectively). The difference between the groups was significant (p<001). One case, confirmed as compartment syndrome, showed marked swelling in the muscle group.

Conclusions Basic ultrasound techniques may be used to identify the site and degree of tissue swelling from cytotoxic envenomation. It is a non-invasive, painless procedure that can assist the clinician to assess the injured limb and may also be of benefit to monitor the progression of swelling.

Key messages

What is known on this subject?
The majority of snakebite presentations in KwaZulu Natal South Africa are caused by cytotoxic envenomation resulting in painful swellings. Such envenomations can cause significant tissue damage and morbidity for patients. The site and severity of this swelling is difficult to pinpoint and quantify. Compartment syndrome, leading to fasciotomy, is easily overdiagnosed clinically.

What this study adds?
This study introduces soft tissue ultrasound as a non invasive, pain free tool for assessing cytotoxic snakebites. Using high frequency ultrasound we have shown that the primary site for tissue damage is the subcutaneous tissues. The muscle compartment is seldom affected and swelling in this area is rare. However, when intramuscular swelling is present the likelihood of a compartment syndrome should be considered.

INTRODUCTION

Snakebite constitutes a significant health problem in the subtropical north-eastern regions of South Africa. We have recently shown that during the hot summer months, 10% of all presentations to a major public hospital ED were due to snakebite (manuscript under review). The venoms of South African snakes fall into three classes. Cytotoxic venoms may cause severe tissue damage with a syndrome of painful progressive swelling that can cause significant morbidity, disfigurement, limb loss and even death. Neurotoxic venoms may result in paralysis and death due to respiratory failure. Two species produce a haemotoxic venom presenting clinically as a major bleeding diathesis; however, such bites are extremely rare. Our own studies in this region indicate that 98% of snakebite admissions are due to cytotoxic envenomation (manuscript under review). Two species, the puff adder (*Bitis arietans*) and the Mozambiquan spitting cobra (*Naja mossambica*), are responsible for most such bites. Both species are widely distributed throughout Africa.

Snake cytotoxins create pores in cell membranes by acting on the phospholipid bilayers resulting in cytolysis.[1] Phospholipase A_2 is one of the main venom enzymes that cause this effect. Others, such as metalloproteinases, cause capillary endothelial damage and cell apoptosis. An inflammatory response to envenomation as evidenced by increased microvascular permeability, early leucocytosis and elevations in interleukins and tumour necrosis factor[2] compounds the problem of painful swelling. The cytotoxicity is similar to that seen in crotaline species in the Americas; however, in contrast with crotaline species, coagulopathy and neurotoxicity are not a typical feature of these bites. Though severe bites may result in systemic haemodynamic compromise, the predominant clinical manifestation in patients bitten by *B. arietans* and *N. mossambica* is an oedematous, bruised and painful limb. The site and degree of swelling essentially determine the resulting pathology and clinical

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picture. However, the severity of the swelling and associated pain may raise the suspicion of an underlying compartment syndrome, which is described as a complication of bites of a number of species with cytotoxic venom, including African vipers,[3 4] North American crotaline species[5 6] and European vipers.[7–10]

Differentiation on clinical grounds may be very difficult. Indeed, in a recent consensus statement from North America it was noted that patients admitted to hospital with crotaline snakebite were five times more likely to undergo fasciotomy if primarily under the care of surgeons, than under the care of medical toxicologists.[11] A recent report has highlighted a high rate of fasciotomy in North America in circumstances where the decision to operate was not adequately supported by objective evidence of compartment syndrome and in the absence of effective antivenom administration.[6] Indeed, a recent North American review has seriously questioned the evidence that fasciotomy is beneficial in snake bite where effective antivenom treatment has been given.[12] Though our experience suggests that the local consequences of bites by African cytotoxic species do not differ significantly from those of crotaline species, we do caution that the effects of local polyvalent sera in reversing these effects is much less well documented than is the case with crotaline Fab antivenom.

Since fasciotomy is associated with significant morbidity, disfigurement and need for subsequent rehabilitation, it is essential that fasciotomy is reserved for patients with a true limb-threatening compartment syndrome, particularly as there is evidence that administration of antivenom may obviate the need for fasciotomy.[11–14] The diagnosis of a compartment syndrome in snakebite is challenging and controversial. An intramuscular compartment pressure (IMCP) below 10 mm Hg is generally accepted as being normal. Muscle perfusion requires an adequate perfusion pressure or *delta pressure*, the difference between diastolic pressure and IMCP. Though various authors have suggested absolute IMCP values ranging from 30 to 50 mm Hg as threshold for intervention, it is believed that the delta pressure is a more valid measure, with a value of 30 mm Hg or less regarded as a marker of critical ischaemia and an indication for a fasciotomy.[15] Absolute values continue to be used however, and an absolute IMCP greater than 30 mm Hg has been incorporated into a North American algorithm for the management of paediatric snakebite.[16] IMCP should ideally be measured directly; this requires however the insertion of a needle into the muscle compartment and is very painful. A validated non-invasive alternative would clearly be preferable.

We hypothesised that ultrasound would provide a useful, non-invasive and painless method to assess the depth and extent of tissue damage following envenomation, and in particular would indicate whether the swelling associated with cytotoxic bites is predominantly centred on the subcutaneous tissues or on the intramuscular compartment with a consequent risk of compartment syndrome. High-frequency ultrasound can clearly differentiate between the subcutaneous tissues and muscle compartments. Most snake bites occur on the limbs, and the unaffected limb can serve as a useful control in assessing the site and degree of damage following a snake bite. A recent report of the use of ultrasound in 13 cases of crotaline (rattlesnake) envenomation suggested that bedside ultrasound might be a useful diagnostic adjunct in the assessment of patients with severe soft-tissue involvement. We report here our experience in 42 patients with cytotoxic limb injury following bites by southern African snakes.

METHODS

The Ngwelezane Hospital Emergency Department Resuscitation Unit (EDRU) is the main referral centre for snakebites in the subtropical north-eastern region of KwaZulu-Natal province, South Africa. This region has a predominant rural population of approximately 3 million people. It has one of the highest incidences of snakebite in South Africa with an annual incidence of 1.18 per 1000 population (manuscript under review).

Patient selection

A convenience sample of patients with snakebite admitted to the EDRU during the summer months from December 2014 to March 2015 were assessed for cytotoxic swelling. All patients with swelling of the upper or lower limb were included and assessed. Patients with minimal or no swelling, bites to other anatomical areas or predominantly haemotoxic or neurotoxic envenomations were excluded from the study. Two trained emergency ultrasonographers performed soft tissue ultrasound on the test subjects. They were blinded to the patient notes, the clinical grading of severity and results of any other investigations.

Assessment method

All admitted patients with snakebite had routine blood tests taken and received baseline standard therapy such as analgesia, intravenous fluids and tetanus toxoid. Admitting doctors followed a department snakebite management guideline (Blaylock 2004). All admitted patients were reviewed within 12 h by an emergency medicine specialist in consultation with a specialist surgeon. The final decision to treat with antivenom (SAIMR Polyvalent Antivenom) was made by an emergency medicine specialist experienced with snakebite management. The decision to perform surgery was made by a surgeon. In a few severe cases patients required both antivenom and subsequent surgery.

The envenomed limb of each patient was scanned at the site of maximal swelling using a Sonosite Nanomax ultrasound machine with a high-frequency (10 mHz) probe (SonoSite, Bothell, Washington, USA). The dimensions of the subcutaneous tissues and the deep muscle compartment were measured in the transverse plane. The unaffected limb was used as a reference control and measured in the same manner. Both images were portrayed simultaneously on a split screen to further confirm that the two sites were comparable. An example is shown in figure 1. The thickness of the subcutaneous tissue and the muscle were measured at the site of maximal swelling in the envenomed limb, and care was taken to ensure measurement at the same anatomical level in the control limb, the distance being measured from the same anatomical reference point in each limb. Since direct measurements are not comparable between subjects differing in size and in site of bite, results were expressed as an expansion coefficient, which we defined as the ratio of the measured thickness of the selected structure in the affected limb to that in the unaffected limb. An expansion coefficient factor of 1 therefore would indicate that both structures were of the same size, with no swelling in response to the bite.

Bias/confounders

Only patients presenting to the EDRU were considered, which excluded any patients from the study population that presented to smaller district hospitals or traditional healers that were not referred on to the Ngwelezane EDRU. These patients may have been less severe not warranting a transfer, did not have transport or potentially could have died.

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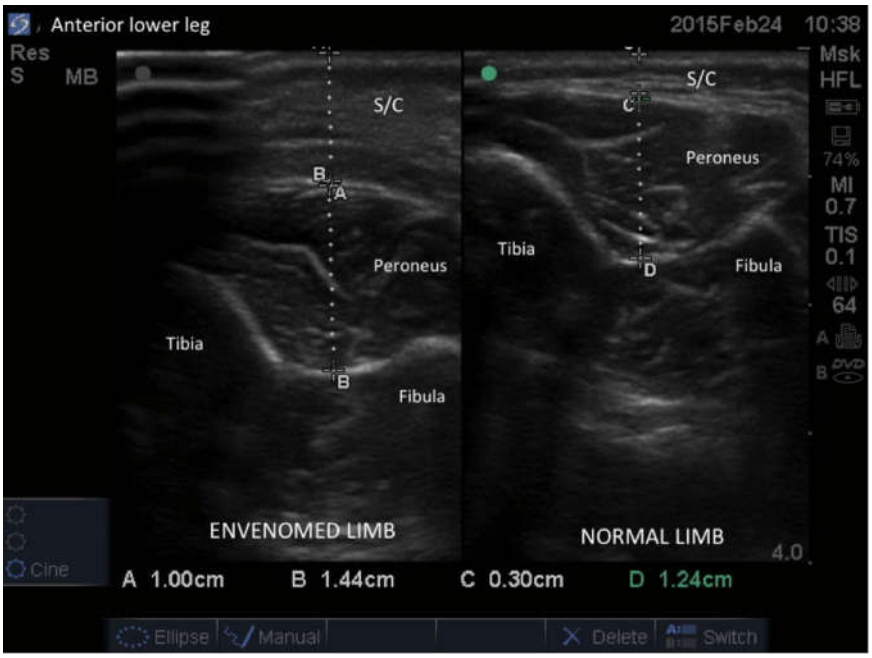

Figure 1 Ultrasound images (split screen) of the anterior compartment (peroneus muscle) of the lower leg. The left panel represents the envenomed limb. The subcutaneous compartment measures 100 mm and the muscle compartment 144 mm. The right panel represents the unaffected limb, scanned at the corresponding anatomical level. The subcutaneous compartment measures 30 mm and the muscle compartment at 124 mm. This would return a subcutaneous expansion coefficient of 3.3 and a muscle expansion coefficient of 1.2.

All data were captured in a Microsoft Excel V.14.4.7 (Microsoft, Redmond, Washington, USA) and statistically analysed using Stata I/C V.13.1 (StataCorp LP, College Station, Texas, USA). The study was approved by the Biomedical Research Ethics Committee of the University of KwaZulu-Natal: Reference BE034/14. Statistical significance between groups was assessed using a Student's t test or analysis of variance as appropriate, and correlations were assessed using Pearson's r coefficient of correlation. A p value of 0.05 was regarded as significant, and 95% CIs are quoted throughout.

RESULTS

We analysed 42 patients with significant cytotoxic envenomation of a limb. Twelve subjects were bitten on the foot, three on the leg, 12 in the hand, 13 in the forearm and two in the upper arm. Seventeen subjects were aged less than 6 years, and a further eight subjects less than 12 and 14 subjects were aged 12 or more. Twenty-four were male and 18 female.

Across the group, expansion of both the muscle and the subcutaneous compartment was noted (figure 2). However, the enlargement of the subcutaneous compartment was significantly greater than muscle. The mean expansion coefficient for the subcutaneous sites was 2.0 (CI 1.7 to 2.3) and for the muscle compartment 1.06 (CI 1.0 to 1.1). The difference is significant ($p<0.001$). Different sites show different rates of increase in subcutaneous expansion coefficient, with median values as follows: foot 1.3 (range 1.0–3.7), hand 1.5 (range 1.1–3.7), upper arm 1.8 (range 1.7–2.0), forearm 1.9 (range 1.1–6.1), leg 3.3 (range 2.9–4.3) ($p=0.04$). Only one patient required a fasciotomy for confirmed compartment syndrome. This patient had the highest observed muscle expansion coefficient at 1.4, and was clearly identified as an outlier (figure 3). We also note from the measured data that swelling continued up to 60 h.

Eighteen patients received polyvalent antivenom and 16 cases required wound debridement, and somewhat surprisingly, there was no correlation between subcutaneous or muscle coefficient and use of antivenom ($p=0.8$ and 0.1, respectively) or between

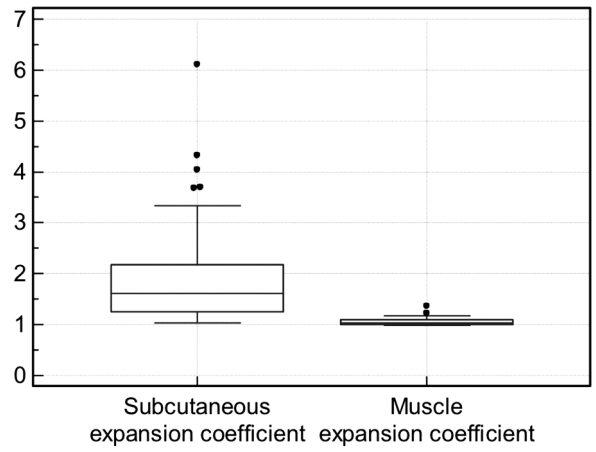

Figure 2 Significant swelling is almost entirely confined to the subcutaneous tissues with minimal involvement of the deep muscle compartment.

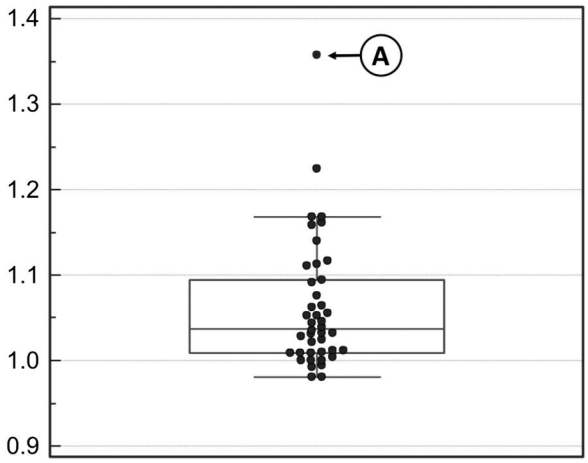

Figure 3 Distribution of muscle swelling ratios among 42 patients. A single patient has a value clearly exceeding those recorded by the group as a whole (labelled A). This patient had a documented compartment syndrome requiring fasciotomy. No other patient suffered a compartment syndrome.

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subcutaneous and expansion coefficient and likelihood of debridement (p=0.25 and 0.2, respectively).

DISCUSSION

All our cases showed a significant subcutaneous tissue swelling, irrespective of site. In most cases there was a small degree of muscle expansion, presumably resulting from diffusion of cytotoxins into the compartment or conceivably even by an extension of the inflammatory response without direct injury. Children were particularly vulnerable to the cytotoxic effects of venom. This may be due to the dose of venom injected in relation to a smaller surface area in the limb. In support of this, evidence has recently been adduced in crotaline bites suggesting a correlation between size and severity of cytotoxicity;[17] as a corollary, it would hold that a smaller victim would be subject to greater injury. We did not show an increased risk of severe intramuscular involvement in children, suggesting that they are not at increased risk of intramuscular envenomation, despite the shorter skin–muscle distance for the fang to traverse. Though children appear prone to a greater degree of swelling, this may be due at least in part to greater elasticity of the skin and subcutaneous tissues, rather than more severe toxicity. This is a point that requires further study.

Significant muscular involvement appeared to be very rare, with only a single case showing a very high muscle expansion factor. This patient had a documented compartment syndrome, and fasciotomy confirmed the presence of necrotic muscle in the lower limb anterior compartment. Animal studies have suggested that direct envenomation of the muscle compartment is necessary to cause a compartment syndrome; injection into the subcutaneous tissues overlying the compartment is insufficient.[18] Most venomous snakes, including *N. mossambica*, have short fangs with an average length of approximately 6 mm. In contrast, *B. arietans* and the gaboon adder (*Bitis gabonica*), both found locally, have fangs of 10–15 mm in length. These fangs have the potential to penetrate through the subcutaneous layer into the muscle compartment. Our experience suggests that this is rare, and for the most part, venom is injected into the subcutaneous tissues. A number of reasons may be hypothesised to explain this: that puff adder bites are infrequent in comparison with spitting cobra bites, that the muscle fascia provides a fibrous barrier to fang penetration, that a defensive bite (typical of the snake striking a human) is not associated with full-depth penetration, and that bites are much more likely to strike the foot or ankle rather than an anatomical site such as the calf with a large intramuscular compartment.

We have shown increasing swelling out to 60 h. There is evidence that delays in treatment of African adder bites substantially increase the risk of serious outcomes, including compartment syndrome, gangrene and amputation.[3]

Ultrasound has been shown to have acceptable accuracy in assessing muscle size when compared with CT and MRI.[19 20] Use of the contralateral limb as a control appears to be acceptable. Differences in muscle size between dominant and non-dominant limbs do not appear to be significant,[21] though there have been reports of a difference of up 7.5% in highly selected groups such as professional sportsmen.[22] Absolute dimensions are of little value in assessment, given the wide variation in thickness of subcutaneous tissues and muscle thickness between individuals, and between anatomical sites. Use of our expansion coefficient will to a degree overcome this, though our results indicate that the potential degree of expansion may be constrained by site, with the leg, for example, offering significantly more space for expansion that the foot. We also note that the muscle compartment is far less tolerant of expansion than the subcutaneous tissues, presumably as a consequence of the constraints offered by the surrounding fascia and perimysium.

Ultrasound is a painless non-invasive means of assessing sites of tissue damage in snakebite. Our clinical experience and observation with cytotoxic envenomation is that the anatomical site of swelling occurs predominantly in the subcutaneous tissues and rarely within the muscle compartment. Ultrasonography has borne this out in the present study. Our findings are in line with those of Vohra *et al*[23] in a small series of 13 crotaline envenomations in North America. In 13 snakebite envenomations, all patients were noted to have subcutaneous tissue swelling while the muscle compartments and fascia were spared. Ninety per cent of patients bitten by crotaline species exhibit local cytotoxicity with erythema, swelling, tenderness and possible myonecrosis. In this the effects appear to be very similar to those of the bites of South African cytotoxic species, the major difference in clinical effect being the relative absence of neurotoxicity and coagulopathy in these South African species.

Although studies in patients with chronic exertion compartment syndrome following exercise have shown a relationship between the change in muscle thickness and the increases in muscle compartment pressures,[24] there is good evidence that muscle size differences do not directly reflect compartment pressures.[21] There may however be a case for using ultrasound to measure muscle size differences as a tool to assist the clinical decision for diagnosing compartment syndrome. The massively swollen, painful and inflamed limb that follows a cytotoxic bite may appear alarming. It is however imperative to differentiate deep muscle expansion from predominantly subcutaneous involvement in order to avoid unnecessary fasciotomy. In our experience, as well as those of others, this point is often insufficiently appreciated.[12–14 18]

Our data do not allow us to establish absolute criteria for the diagnosis of a limb-threatening compartment syndrome following snakebite. Nor may this be possible on morphometric analysis alone. A recent study of patients with lower limb injury failed to find any correlation between thickness of muscle and intracompartmental pressure, possibly resulting from differences in soft tissue elasticity among patients.[21] However, our results do suggest a useful role for ultrasound. It appears effective in identifying the subcutaneous tissues as the major site of envenomation, which would offer a degree of reassurance that a compartment syndrome is unlikely. It also suggests that higher values of the muscle expansion coefficient may have some correlation with an increased risk of compartment syndrome, given that the single such case in our study had a muscle expansion coefficient, which was clearly an outlier. At the current time it is appropriate to monitor such patients by direct physical examination and compartment pressure sampling.[5] An important caveat raised by our results, however, is that a decision to undertake fasciotomy should not be based on the extent of swelling alone: such swelling is predominantly subcutaneous, easily mistaken for a compartment syndrome[25] and clinical or Doppler evidence of vascular compromise or direct observation of intracompartmental pressure is required.[5 6 11 13 16 18]

In conclusion, we propose that basic ultrasound techniques may be used to identify the site and degree of swelling from cytotoxic snake envenomation. It is a quick and painless procedure that can provide the clinician with valuable insights into the extent of soft tissue damage. Significant subcutaneous oedema may warrant consideration for antivenom treatment and a sizable increase in affected muscle bulk should alert the clinician to a possible compartment syndrome. Furthermore, using this

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technique, clinicians are able to monitor swelling progression and the response to antivenom treatment.

Limitations

Ultrasound assessment of the included patient sample was only done at one time, soon after admission. Repeated ultrasound assessment of the affected limb would provide more dynamic data that could better describe the progression of swelling over time. Such an approach would also identify the time of maximum swelling following envenomation.

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Competing interests None declared.

Patient consent Obtained.

Ethics approval Biomedical Research & Ethics Committee of the University of Kwazulu Natal.

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CHAPTER 7

Synthesis and discussion

SYNTHESIS AND DISCUSSION

SNAKEBITE AS A MEDICAL AND PUBLIC HEALTH PROBLEM IN NORTH-EASTERN KWAZULU-NATAL

Pilot study: scale of the problem and preliminary clinical observations

Severe snakebites in northern KwaZulu-Natal: Treatment modalities and outcomes (Chapter 2)

Our initial descriptive study on snakebite presentations to the Ngwelezane Hospital Emergency Department **[16]** suggested the value of further research on snakebite in north-eastern KZN, given the high incidence (Chapter 2). Some important observations were made such as a clear seasonal trend for snakebites, a high rate of anaphylaxis from antivenom and the apparent vulnerability of children. The results of this study were similar to earlier reports in this region **[13,15,17,60]**. It was clear that little progress has been made in preventing and managing snakebites over the previous decades. This exploratory study prompted the current project.

Current information on the incidence of snakebite is based on reports from government departments and global organisations such as the World Bank, World Health Organization (WHO) and the United Nations; it tends to be painted with a broad brush on a country or regional basis **[3,5]**. Though these data are supported by numerous published studies from hospital records and local surveys in communities affected by snakebite, there is no overall uniformity in reporting and the detail required to plan public health services at sub-regional level within countries is frequently lacking. In South Africa, snakebite is not a notifiable disease. Most victims of snakebite are treated within the public health sector, which does not have effective systems for aggregating of disease data, most information being retained within each hospital's records department. In areas of KZN and the other two eastern provinces of Limpopo and Mpumalanga, as well as in neighbouring countries such as Zimbabwe and Mozambique, the incidence of snakebite is clearly significant yet no accurate data on incidence or the rate of hospital admission are available.

Determining the disease burden of snakebite and the costs to health care

Estimating the burden of snakebite on public hospitals in KwaZulu-Natal, South Africa (Chapter 3).

We therefore undertook the study described in Chapter 3, which is the first to attempt to estimate the frequency of admissions for snakebite in the province with any accuracy. Given the extreme variability in the standard of record-keeping within individual hospitals and the lack of centralised or standardised reporting, we hypothesised that a system based on the extrapolation of use of antivenom (for which good records are kept in the provincial health department's central pharmacy depot) would allow a crude but reasonably accurate estimate on the epidemiology of snakebite, with the critically important information of the ratio of antivenom ampoules dispensed to actual numbers of patients being determined by an analysis of usage in a number of representative institutions with reliable record-keeping. We believe that this is a novel approach. This study clearly established that within KZN snakebite incidence varies widely. We noted that the low-lying, subtropical coastal areas have a significantly higher incidence than theinland regions, the subtropical north-eastern region (where Ngwelezane Hospital is situated) has a much higher incidence than the southern parts of the province, and rural areas are more affected than urban. From these data we were able to estimate health care costs, and have shown that snakebite imposes a significant burden on healthcare. This provides, for the first time, reliable information which may be used by health planners to implement snakebite prevention programs and to plan effectively for the medical care of victims of snakebite, thus providing appropriately targeted resources for managing what is widely recognised to be a neglected disease **[1,5,50,70]**.

Limitation and future research

There are limitations to the studies. In the absence of detailed and accurate information from every health facility within the Province, we developed a model which relies on extrapolation; as such certain assumptions are necessary: that the sites from which our data are drawn are truly representative of the province as a whole, and that the formula we derived relating admissions to treatments, and treatments to ampoules of antivenom dispensed is robust enough to apply on a wider scale. We would not have captured patients

who did not present to public hospitals, but may have sought help from traditional healers **[13]** or from the private health care sector. Large-scale community surveys are required to estimate this number. It is however our impression that most patients suffering a significant bite will seek medical attention; furthermore, the demographics of the patients experiencing bites however are such that they normally make use of the free or subsidised medical care offered in public hospitals and not in expensive private clinics. We have now approached researchers in Public Health affiliated to the University of KZN, such as the Africa Centre based near Mtubatuba in the heart of the high incidence snakebite region, with a view to undertaking collaborative community-based research on snakebite.

MANAGEMENT OF SNAKEBITE, RISK FACTORS FOR SEVERITY AND PREDICTION OF THE NEED FOR INTERVENTION

Clinical and demographic data and factors predicting severity

Snakebite in north-eastern South Africa: Clinical characteristics and risks for severity (Chapter 4)

Ngwelezane Hospital is the major referral centre for snakebite in the high-incidence north-eastern region of KZN. Our prospective study documented the extreme seasonality of snakebite and the significant disease burden experienced by the hospital in the hot, wet summer months, supporting findings from our earlier study **[16]** (Chapter 2), as well as those of others from the same area **[14,15,17,18,71]**. We showed that, in contrast to popular perception, neurotoxic envenomation leading to progressive muscular weakness constitutes a very small percentage of all admissions, with 98% of admissions resulting in painful progressive swelling following cytotoxic envenomation, as previously suggested in these earlier reports. Haemotoxic presentations were extremely rare; such a case has recently been reported from Ngwelezane Hospital **[38]**.

We identified a number of risk parameters which appear to correlate with the need for more aggressive treatment including paediatric age group, delayed presentation and disturbed haematological parameters such as low platelets, low haemoglobin, raised INR and reduced

or raised white cell counts. Similar risk parameters have been identified in other parts of the world, albeit in different snake species **[48,72-75]**. We showed however that individually they are too poorly predictive to be of value in algorithms of management.

Limitations and future research

Although this is the largest descriptive analysis of snakebites done in South Africa, the study is limited in that it represents only one hospital. It is also limited in that the medical staff at Ngwelezane hospital have extensive experience with snakebites imposing a positive bias on outcomes and the effects of treatment. This unfortunately is not replicated throughout the country. Multicentre studies using pooled data would provide a more accurate assessment of the current status of the management of snakebite; there is also the potential for meta-analysis and systematic review. It is also critical that more information is made available for sub Saharan Africa as a whole and southern Africa, including the countries neighbouring South Africa in particular.

We identified some intriguing demographical data which had not emerged previously, including the disproportionate risk in the second and third decades of life with some variation between the peak age at risk between males and females, albeit that the crude risk is similar. There is a dire lack of information on the snake-human interactions which lead to snakebite (including a more nuanced understanding of snake behaviour), an area which offers substantial potential for research and which may be critical in reducing the incidence of snakebite.

The Zululand severity scoring system

Classifying snakebite in South Africa: Validating a scoring system (Chapter 5)

Scoring systems to aid in the management of snakebite have been developed elsewhere, particularly in North America **[48,76,77]**. No such research has been attempted in Africa. Building on information gained from our two earlier studies (Chapter 2, Chapter 4), we identified 6 non-clinical demographic and haematological parameters that when abnormal correlated with a need for more aggressive treatment, which we termed Active Treatment Interventions (ATI). These included age < 12 years, delay to admission > 6 hours, abnormal blood results such as haemoglobin, platelets, INR and white cell count. ATI was selected

as the primary end point since true severity is difficult to determine in snakebites on admission, especially since many progress from mild to moderate to severe over time. Using these risk predictors in the same 5-year patient cohort, we developed a scoring model that showed 4 or more risk predictors predicted the need for ATI with a reasonable degree of accuracy. These risk predictors were validated prospectively on a new patient cohort. The score, which we have named the Zululand Snakebite Severity Score (ZSSS), is of particular value in those cytotoxic snakebites that are classified as mild to moderate in severity but have the potential to progress to a more severe outcome. By scoring a patient using the identified risk predictors the doctor can predict with 80% accuracy which patients are likely to require additional such an active treatment intervention. Thus more confidence can be placed on a decision to prescribe antivenom earlier rather than later, and in doing so, reduce the morbidity and potential mortality of a patient. The ZSSS can potentially augment the clinical assessment made by the doctor to make a more accurate diagnosis in snakebite patients especially those with mild to moderate signs. We have now incorporated the ZSSS into our treatment algorithm, where it will play the restricted but important role of focusing the clinician's attention on those patients with cytotoxic swelling who are at greatest risk of progression, and alerting them to the possible need for early antivenom administration.

Limitations and future research:

This study is limited by the setting of the validation cohort. We used the same hospital to validate our risk parameters for severity, albeit it prospectively. In order to strengthen the ZSSS, further validation studies should be conducted by separate investigators in other settings in South Africa. A true reflection of severity would most likely best be correlated to the species of snake. The end point of an acute treatment intervention can only act as a surrogate for severity since it relies on the doctor's experience and clinical judgement to grade the bite. We plan to take this forward by developing a research project to analyse the blood of envenomed patients and identify species-specific venom proteins immunologically to identify the snake species, as increasingly practised elsewhere **[78]**. The species can then be correlated with the clinical presentation and outcome of the patient; this may potentially have important clinical value.

The site of swelling following cytotoxic snakebites

Ultrasound findings in 42 patients with cytotoxic tissue damage following bites by South African snakes (Chapter 6)

The future course of cytotoxic swelling in the snakebite victims is difficult to predict since it is progressive. This has implications for both antivenom administration and for the need for surgical intervention, particularly fasciotomy, which in our opinion and that of authorities is in many cases too readily performed **[23,24,27,79,80]**. Whereas invasive methods for the confirmation of compartment syndrome requires skill and are extremely painful and uncomfortable for the patient, ultrasound suggested itself as a readily available tool that may assist in the decision on the need for intervention.

Our results suggest that, the extent of swelling is no guide to the anatomical site of that swelling, and therefore offers little information to guide a decision for fasciotomy. Indeed, we showed that the cytotoxic tissue damage following envenomation almost invariably occurs in the subcutaneous tissues, with little risk to the underlying muscle compartment. This supports the majority view that a prophylactic fasciotomy in severe cases is unnecessary and may cause significant morbidity **[27,81-83]**. The clinical picture is typically misleading, but the actual site of painful swelling is readily identified on soft tissue ultrasound and can effectively be treated with early antivenom. Ultrasound has potential as a useful tool to assess the site and degree of swelling in snakebite, and therefore to guide treatment.

Limitations and future research:

We did not determine intra-compartment pressures directly and correlate these with the ultrasound findings, though in terms of assessing clinical utility, this is probably not necessary as none of our patients with subcutaneous swelling developed a compartment syndrome. In this study, we performed a single ultrasound examination: as a follow-on, we wished to perform serial examinations since swelling in cytotoxic envenomation is a dynamic process, thus learning more about the course of the tissue damage. Furthermore, we believe it would be very interesting to know with a deep injection into the muscle compartment is restricted to certain species only; in our environment both the puff adder and the gaboon adder have fangs which may approach 5 cm in length and are therefore

eminently capable of a deep bite, whereas those of the Mozambique spitting cobra are very much shorter. Such a correlation will require more accurate determination of the species of the biting snake than has been possible thus far...

CONCLUSION

We used a variety of approaches to provide a better understanding of snakebite in KZN. Several interesting lines of further investigation have become apparent and research on neglected this disease will continue.

We will build on the information we have gained to assist the provincial health authorities in developing a formal strategy for the prevention and management of snakebite and the limitation of the serious sequelae which may arise from such bites. We are developing the framework for such a strategy and an expert peer-reviewed process for the development of official guidelines on treatment protocols for snakebite in South Africa is planned.

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