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# CLINICAL UPDATE

# Managing snakebite

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#### What you need to know

- Bites from venomous snakes can result in bleeding, paralysis, long term disability, and death
- Immobilise the bitten limb when transporting the patient to a medical facility; the universal use of pressure immobilisation is controversial, and tourniquets are not recommended
- The 2o-minute whole blood clotting test is a simple bedside test to screen for and monitor coagulopathy in resource-limited settings
- Assess vital parameters and initiate resuscitation measures if the patient is clinically unstable with signs of bleeding, shock, paralysis, or respiratory distress
- Intravenous antivenom is recommended in patients with systemic symptoms; the dose and type depend on likely snake species, local guidelines, and availability

Snakebite affects between 1.8 to 2.7 million people worldwide each year, and it is estimated to cause between 80 000 and 138 000 deaths.<sup>12</sup> A mixture of toxins (venom) is injected into the body following bite by a venomous snake.<sup>3</sup> Envenoming can be a highly dynamic clinical event. Symptoms can progressively worsen to a life-threatening emergency. Snakebites can have long term physical sequelae such as amputation, paralysis and disability, and psychological health consequences.<sup>4</sup>

Snakebite envenoming is more common in South and South-East Asia (2 million annually), sub-Saharan Africa (420 000) and Latin America (150 000).<sup>12</sup> These regions also report a high burden of deaths from snakebite (100 000, 32 000, and 5000 deaths respectively) possibly due to poor access to medical aid.<sup>12</sup> Delayed diagnosis and treatment can worsen prognosis.<sup>8 -11</sup> The World Health Organization recognised snakebite as a neglected tropical disease in 2017 and called for concerted global action to reduce deaths and disability.<sup>12</sup>

In this clinical update, we present an approach to evaluation and management of snakebites for primary care providers in resource-limited settings in endemic regions. The principles of management are broadly similar, but it is beyond the scope of this article to cover clinical syndromes and management for the varied snake species globally.

#### Sources and selection criteria

We searched the Cochrane Library, Google, and PubMed, using the MeSH terms: "(snakebite, diagnosis and treatment guidelines) and (snake, scientific names of individual snake species, snakebite, envenoming, venom, and antivenom)". Research papers and case reports from Latin America, South and South-East Asia, and sub-Saharan Africa were retrieved. There were no language restrictions. Additional articles were obtained by citation tracking of review and original articles. Although the search focused on key papers published in the past five years, older publications of importance have been included. The review also drew from the widely established African and South-East Asian regional guidelines on the treatment and prevention of snakebite envenoming.

### Who is at risk of snakebite?

Rural communities in tropical countries are worst affected.<sup>13 -16</sup> Agricultural workers, hunter-gatherers, herders, fishermen, and rural families living in precarious housing conditions with outdoor toilets have a higher risk of snakebite. Their living environments intersect with snake habitats.<sup>12</sup> Men between 10 and 40 years are more commonly affected.<sup>4 15 17 -20</sup> Non-mechanised farming techniques, barefoot farming, and sleeping on the floor further increase the risk.<sup>16 21</sup> Bites are more common during wetter months, when agricultural activities and breeding season for snakes potentially converge.<sup>15 17 20 22 23</sup>

### How does envenoming occur?

Most medically important snakes in these regions belong to two taxonomic families<sup>24-27</sup>:

- *Viperidae*—African adders and bush vipers, Asian pit vipers, mamushis, habus, and New World rattlesnakes, moccasins, bushmasters, and lanceheads
- *Elapidae*—African and Asian cobras, African mambas, African rinkhals, Asian kraits, Australian and Papuan venomous snakes, Asian and New World coral snakes and sea snakes

Venomous snakes inject venom during a bite using specialised grooved or hollow teeth called fangs. The fangs are connected to venom glands on each side of the upper jaw via a duct.<sup>28</sup> Viperids usually have long foldable front-fangs, while those in elapids are short and fixed (fig 1).<sup>28</sup> Depending on fang length, venom is introduced either subcutaneously or intramuscularly.<sup>3</sup>



Fig 1 | Difference in fangs between elapids and viperids. A) Elapids have short, fixed, front fangs. B&C) Vipers have much longer and retractable front fangs. (Photos courtesy of Ahmad Khaldun Ismail)

Some snakes with fangs towards the back of the mouth ("non-front-fanged colubroids" such as African boomslang and vine snakes, South American racers, and Asian yamakagashis) and the burrowing asps (or stiletto snakes) whose unique jaw kinesis coupled with exceptional neck flexure allow for a single protruding fang to be jabbed sideways or backwards, can also cause envenoming.<sup>3 28 29</sup> Spitting cobras and rinkhals can eject venom over several metres, often delivering venom droplets into the eyes of the animal or human perceived to be a threat.<sup>30 -32</sup>

### What are the clinical effects of snakebite?

Not all people with a snakebite have clinical symptoms. Often bites are by non-venomous snakes. Sometimes venomous snakes do not inject venom during a bite.<sup>33</sup>

Clinical manifestations vary between species of snakes (see box 1).<sup>3</sup> Some toxins in venom exert local effects such as swelling, blistering, bruising, and necrosis at the bite site.<sup>24 25</sup> Other toxins can be distributed systemically through lymphatics and blood vessels and act at distant sites. See supplementary text for an overview of important sites and pathophysiology of venom-toxin action. Common systemic effects include bleeding, paralysis, generalised rhabdomyolysis, and acute kidney injury. Venom injection deep into a limb can cause tissue swelling in the tightly constrained space and compromise neurovascular function.<sup>54 55</sup> This manifests as "acute compartment syndrome."<sup>24 25 31</sup>

#### Box 1: Clinical effects of snakebite

#### Local effects

- Bite site—Swelling, blistering, bruising, necrosis (usual after bites by cobras and vipers, with some exceptions in each family, and burrowing asps)<sup>24 25</sup>
- Acute compartment syndrome after deep bite into a limb—Intense pain, abnormal sensations, or a cold, pulseless, immobile limb<sup>24</sup><sup>25</sup>
- Venom ophthalmia from entry of venom droplets or spray into the eyes—Intense pain, redness, blepharitis, blepharospasm, and corneal erosions<sup>31</sup>

#### Systemic effects

- Vascular—Envenoming by most viperid and Australopapuan elapid species and some non-front-fanged colubroids can trigger clotting failure, platelet abnormalities, and vessel wall damage.<sup>34-36</sup> Effects range from clotting test abnormalities to mild bite site or mucosal bleeds to severe spontaneous systemic or intracranial haemorrhage<sup>24 25</sup>
- *Shock*—From bleeding or plasma extravasation systemically or into the swollen, bitten limb, myocardial dysfunction, pituitary bleeds, vasodilation, sepsis, and anaphylaxis<sup>29 36 -42</sup>

- Neuromuscular—Most elapid and some viperid venoms can cause paralysis by action at the nerve (presynaptic) or muscle fibre (postsynaptic) of the neuromuscular junction.<sup>24</sup> <sup>25</sup> Weakness of eye muscles initially present as ptosis, diplopia, and blurred vision. This is followed by sequential weakness of bulbar (dysphagia, dysphonia, and drooling), neck, respiratory, and limb muscles<sup>43</sup>
- Generalised muscle destruction is caused by envenoming by sea snakes and some elapid and viperid species.<sup>24 25</sup> This manifests as muscle pain and tenderness, especially of the neck, trunk, and proximal limbs with dark urine<sup>29</sup>
- Acute kidney injury likely results from secondary effects such as hypotension, fibrin-platelet microthrombi in capillaries and arterioles, and immune or haem related tubular damage, or directly from effect of venom<sup>44-53</sup>

# How do patients present?

Patients usually give a history of being bitten by a snake, except those who experience painless nocturnal bites by kraits while asleep.<sup>22 56 57</sup> Patients are often fearful and anxious. Occasionally, painful bites may be mistaken for a puncture wound from a thorn or sharp stone and be ignored initially.<sup>58</sup> Some patients, especially children, bitten by highly venomous snakes, may present with cardiovascular collapse, unconsciousness, bleeding, paralysis, or respiratory failure and may not provide a clear history of snakebite.<sup>44 59</sup> It is important to consider envenoming in these situations in regions where snakebites are common.<sup>24 25</sup>

Nausea, vomiting, abdominal pain, and headache are non-specific symptoms but must be monitored as these may herald serious complications such as uraemia, acute pituitary or intracranial bleeds, and anaphylaxis.<sup>24</sup>

# What first aid can be provided?

Reassure the person about prompt first aid and medical assistance to allay fears. Arrange for rapid transport to the nearest medical facility, preferably with access to antivenom and critical care support.<sup>60</sup>

Immobilise the person, and especially the bitten limb to slow venom spread.<sup>24</sup> Remove rings and other tight objects around the limb.<sup>61</sup> A systematic review identified pressure immobilisation with an elastic bandage or pad (at a comfortable pressure) at the bite site as an effective first aid measure to slow venom spread, but the quality of evidence was very low.<sup>62 63</sup> Its use is variable, and it is discouraged in most practice and guidelines because of the uncertainty of benefit and possibility of worsening local tissue damage.<sup>15 29 62 64 ·67</sup> However, pressure immobilisation is generally recommended for neurotoxic elapid bites in some regions.<sup>68</sup> Its

clinical efficacy and risk of worsening soft tissue injury in local envenoming have not been adequately assessed.<sup>24</sup> <sup>29</sup> <sup>66</sup> <sup>69</sup> A small study (15 patients) in Myanmar found that pressure pads were effective in reducing venom spread in Russell's viper bite, and local effects after pad application were no more severe than those before treatment.<sup>70</sup>

Tourniquets can cause severe local damage and gangrene and must not be used.<sup>24,25</sup> It is common for communities to resort to traditional therapies such as wound incisions, cauterisation, and application of herbs, minerals, or animal excrement. These can delay access to effective treatment and may cause more harm.<sup>15,71,72</sup> Irrigate eyes with copious amounts of water if there is exposure to venom.<sup>31</sup>

### What to cover on initial assessment?

Rural and remote primary care centres are often the first point of medical aid for people with a snakebite. Laboratory and intensive care services at such facilities are often limited. A competent clinical assessment is vital to guide management and referral decisions.<sup>14</sup> 73 -76

Snakebite envenoming can quickly worsen into a life-threatening emergency. Assess vital parameters to identify if the patient is critical or at risk for shock, respiratory failure, and cardiac arrest.<sup>2425</sup> Published severity scores for snakebite are unreliable.<sup>3</sup> The Glasgow coma scale score and pupillary reactions can be misleading in patients with advanced paralysis who are unable to open their eyes or respond to painful stimuli and should be avoided in these circumstances.<sup>24</sup>

#### History

Reassure clinically stable patients. Ask about their symptoms to determine the presence, nature, and extent of envenoming. Details about the site, circumstances, and timing of the bite can reflect distinctive features of epidemiology, habitats, and periods of activity of medically important snakes locally and help infer likely biting-species.<sup>3 24 25</sup>

Inquire about medications, substance use, and comorbidities as these can influence diagnosis and outcomes. Recent ethanol or recreational drug use may modify presenting symptoms. Antiplatelets or anticoagulants may worsen bleeding and interfere with key blood tests. Shock in patients with pre-existing coronary artery disease can precipitate a myocardial infarction.<sup>3</sup>

### Examination

*Bite site*—Look for fang marks, retained fangs, bleeding, swelling, bruising, discoloration, and blisters.<sup>24</sup> Fang marks do not confirm snakebite since bites by lizards, fish, rodents, large spiders, and some insects and thorns also leave paired punctures.<sup>3</sup> Their absence does not preclude envenoming, as many snake species produce faint or undetectable bites.<sup>22 24 25 56 77 78</sup> Raised vertical, red, tender

streaks on the bitten limb suggest lymphangitis.<sup>3 24 25</sup> Regional lymph nodes may be enlarged and tender with bruised overlying skin.<sup>3 24 25</sup> Note any tourniquets, ligatures, wound incisions or cauterisation, and local traditional remedies as these may lead to specific complications requiring management.<sup>24 25</sup> For instance, tourniquets and ligatures, if left on for long, can cause severe local damage including ischaemia, necrosis, and gangrene. Similarly, incisions and local applications can lead to local bacterial infections, sepsis, and tetanus.<sup>18 79 80</sup>

*Systemic examination*—Look for signs of coagulopathy such as sub-conjunctival, retinal, nasal, and gingivobuccal bleeds, ecchymoses and internal haemorrhage (such as intracranial, pericardial, pleural, and retroperitoneal).<sup>24,25</sup> Assess extraocular movements, bulbar function, and muscle power.<sup>24,25</sup> Look for ptosis, muscle tenderness, and jaw stiffness.<sup>24,25</sup> Jaw stiffness is a prominent but often overlooked feature in sea snake envenoming that, unlike trismus, can be reduced by sustained pressure on the lower jaw.<sup>81</sup>

*Identifying snake species*—Occasionally patients or accompanying persons may bring the killed snake for identification or have a picture of it. A herpetologist can be consulted to help identify the species.<sup>29</sup> Identification of snakes based on description by victims or recognition from pictures is often unreliable.<sup>29 82 83</sup> Identifying biting-species helps avoid unnecessary antivenom in patients bitten by non-venomous snakes or by species whose venoms are not neutralised by available products. It can help select appropriate antivenom in countries with products specific against single species and anticipate clinical progression. However, delaying emergency treatment until the species is identified is unnecessary.

Knowledge of local snake species, comparison of clinical effects in the patient against established species-specific syndromes, and consideration of the circumstances and timing of the incident can help infer likely biting species.<sup>29 82</sup> This approach is widely used to guide treatment with polyspecific antivenom in endemic areas of Africa and Asia.<sup>82 84</sup> Snake identification tests based on venom antigen are valuable research tools but are currently unavailable for routine clinical use except in Australia.<sup>85</sup>

### What tests can be performed?

Perform a baseline 20-minute whole blood clotting test (20WBCT) to screen for coagulopathy in patients without overt bleeding. The 20WBCT is a simple, rapid, and inexpensive bedside test to screen for and monitor coagulopathy in areas with limited access to emergency laboratory facilities.<sup>29 86 87</sup> Collect a sample of venous blood from the patient and place a few millilitres into a clean dry test tube. Leave it undisturbed for 20 minutes at ambient temperature. Unclotted blood that runs out or a friable clot that readily breaks down on tipping the tube once at 20 minutes indicates a possible clotting disorder (fig 2).<sup>24 25</sup>

B



Fig 2 | Examples of the 20-minute whole blood clotting test. A) With normal blood, a clot is seen at 20 minutes after sample collection. B) Incoagulable blood at 20 minutes, from a patient with Russell's viper envenoming

Most clinical validation studies on the 20WBCT report a sensitivity of 82-89% and specificity of 82-98%. One study indicated that the test might potentially miss one of every five coagulopathic patients. <sup>88 89</sup> A recent systematic review and meta-analysis of the 20WBCT to evaluate its accuracy in detecting coagulopathy (defined as INR >1.4 or fibrinogen <100 mg/dL) revealed an 84% sensitivity and 91% specificity using the international normalised ratio (INR) as reference standard and 72% sensitivity and 94% specificity using plasma fibrinogen as reference standard.<sup>90</sup> The test was less sensitive in detecting milder coagulopathy (median INR for patients with a false negative 20WBCT was 1.9 (IQR 1.6 to 12, skewness of 1.06 and kurtosis of -0.83) and resolution of coagulopathy following antivenom administration (sensitivity 5% to 67%).

In settings with laboratory support, additional tests might include a complete blood count, coagulation studies, and biochemical assays including creatinine phosphokinase (CPK), serum creatinine, blood urea, and electrolytes.<sup>3</sup> A low haematocrit usually occurs with blood loss. Higher than normal values may indicate haemoconcentration from systemic plasma extravasation. Peripheral neutrophilic leucocytosis represents a general inflammatory response and confirms systemic envenoming. Severe thrombocytopenia contributes to bleeding diatheses. It may indicate microangiopathic haemolysis when accompanied by schistocytes in the blood film and acute kidney injury. Prothrombin and activated partial thromboplastin times, D dimer, fibrinogen, and fibrin degradation products are more sensitive indicators of venom induced clotting disturbances. Blood urea, serum creatinine, and electrolyte concentrations help screen and monitor acute kidney injury. CPK levels above 10 000 units/L indicate severe rhabdomyolysis. Unexplained hypoglycaemia (venous blood glucose <55 mg/dL) can be an important clue to acute hypopituitarism following snake envenoming.<sup>91</sup>

# How is snakebite managed?

# Resuscitation and supportive care

Admit all snakebite patients for observation for a minimum of 24 hours. The onset of symptoms may be delayed but can worsen rapidly. Inform patients and/or their relatives about potential complications, treatment, and critical-care measures using simple language, after emergency medical stabilisation. If required, explain the need for referral clearly.

Promptly manage airway obstruction, respiratory paralysis, and shock by restoring airway, oxygen, intubation, and assisted ventilation as needed, and intravenous fluids. Figure 3 summarises the management of snakebite. Choose sites of venous access such as the hands, wrists, and in some cases the feet where haemostasis by external pressure is most likely to succeed.<sup>24</sup> Avoid central venous or arterial punctures before establishing a negative 20WBCT.<sup>24</sup> Ensure that an intravenous line and resuscitation facilities are in place before releasing tourniquets, since this may trigger pronounced clinical deterioration.<sup>92</sup> Avoid aspirin or other NSAIDs to control pain as they can exacerbate bleeding diathesis.<sup>3</sup>



Monitor vital parameters and urine output at regular intervals in all patients. The 20WBCT can be repeated as it is sometimes negative initially, and coagulopathy may be detected later.<sup>24 25</sup>

#### Antivenom

Guidelines from the WHO recommend antivenom treatment for patients with shock, spontaneous systemic bleeding, uncoagulable blood, neurotoxicity, black urine, acute kidney injury, rapidly progressive local swelling, and bites by species known to cause local necrosis and digital bites.  $^{\rm 24\,25}$ 

Antivenoms are whole or fragmented immunoglobulins fractionated from the plasma of domesticated animals hyper-immunised with venom from one or more snake species over variable periods.<sup>93</sup> They are highly specific and will neutralise only the venoms used in their production and those of a few closely related species.<sup>93</sup> Polyspecific Early administration of antivenom prevents or limits haemodynamic alterations, progression of coagulopathy to clinically overt bleeding, postsynaptic neurotoxicity, myotoxicity, acute kidney injury, and local tissue damage.<sup>24 25 94</sup> Physiological levels of clotting factors are at least partially restored within a median of six hours with sufficient doses of specific antivenoms.<sup>45 95 -101</sup>

Robust clinical data on the safe and effective initial dose of antivenom are lacking for most products.<sup>102</sup> Clinicians often rely on manufacturers' recommendations provided as package inserts or labels, but these can be unreliable.<sup>103 104</sup> We suggest following national protocols or standard regional guidelines for dose.<sup>24 25</sup> Administration is always intravenous, as bolus or diluted in saline solution over 10-60 minutes, at the same dose for adults and children.<sup>24</sup> Repeat administration of antivenom if bleeding persists, if weakness or cardiovascular signs worsen within two hours, or if a 20WBCT is positive at six hours after antivenom administration.<sup>3</sup>

The effectiveness of antivenoms in treating established neurotoxicity, soft tissue damage, and acute kidney injury is not established.<sup>24 25 94 105 106</sup> Additional treatments are indicated for these.

# Other treatments

Neostigmine with atropine is a potentially useful adjunct in patients bitten by snakes such as some cobras with postsynaptic neurotoxins in their venom. Its use must never delay or preclude antivenom treatment or intubation.<sup>24</sup>

Administer a tetanus toxoid booster in all patients except in those with coagulopathy, in which case injection is postponed until haemostasis is achieved.<sup>3</sup> Aspirate large tense bullae to facilitate nursing the bitten limb, pre-empt spontaneous rupture, and prevent secondary infection. Broad spectrum antibiotics are indicated only if the wound has been incised or there are signs of necrosis, wound infection, or abscess formation.<sup>3</sup> Surgical debridement or amputation of gangrenous digits or limbs and skin grafting may be needed.<sup>24 25</sup> Fasciotomies are rarely justified since compartment pressures usually remain within normal limits.<sup>3 107</sup>

# Risk of adverse reactions with antivenom

Monitor patients for adverse reactions in the first two hours of antivenom administration (box 2).<sup>29</sup> Anaphylaxis or pyrogenic reactions occur early (within minutes or hours). Mechanistic studies suggest that most events are not IgE mediated and thus cannot be accurately predicted by skin tests for immediate hypersensitivity.<sup>109</sup> However, their incidence and severity can be reduced by a prophylactic subcutaneous injection of low dose adrenaline.<sup>108</sup> <sup>110</sup> Pyrogenic reactions result from product contamination during manufacture.<sup>111</sup>

# Box 2: Clinical features and frequency of adverse reactions to antivenom

## Anaphylaxis symptoms

- Itching
- Urticaria
- Nausea, vomiting, abdominal pain, and diarrhoea
- Life threatening shock, bronchospasm, and angioedema<sup>108</sup>

## **Pyrogenic reactions**

These present with fever, rigors, and vasodilation with or without hypotension

## Late or serum-sickness type reactions<sup>24</sup>

- Fever
- Nausea, vomiting, diarrhoea
- Itching or recurrent wheals
- Joint and muscle aches or joint swelling
- Lymph node enlargement
- Proteinuria and kidney disease

Depending on the dose, speed of administration, and product quality, the risk of any early reaction varies from 3% to more than 80% in studies from Latin America and South Asia. About 5-10% of such events are associated with life threatening consequences.<sup>29</sup> 98 108 110 112 The incidence of fatal reactions is unclear because of confusion with symptoms of envenoming, but some have been reported.<sup>112</sup>

Treat anaphylaxis at the earliest sign.<sup>24 25</sup> Suspend antivenom administration and inject adrenaline intramuscularly, ideally into the upper lateral thigh.<sup>24 25</sup> Additional treatment includes intravenous antihistamines and glucocorticoids and inhaled bronchodilators for bronchospasm.<sup>24 25</sup> Anaphylaxis can recur, and glucocorticoids do not prevent recurrence.<sup>112</sup> On resolution of the episode, cautiously resume antivenom in patients with a definite indication for continued treatment.<sup>24 25</sup> Treat pyrogenic reactions with physical cooling, antipyretics, and intravenous fluids.<sup>24 25</sup>

Late reactions may manifest a week after administration.<sup>108</sup> <sup>111</sup> <sup>113</sup> Their incidence varies widely from 5% to 56% in observational studies and trials using differing diagnostic criteria.<sup>108</sup> WHO guidelines recommend a five-day course of oral antihistamines for those with serum-sickness type late reactions, and a five-day course of prednisolone in those who fail antihistamine therapy after the first two days.<sup>24</sup> <sup>25</sup>

# Whom to refer?

Patients with persistent bleeding despite repeated antivenom treatment or having respiratory and renal failure may require urgent supportive measures such as blood transfusion, mechanical ventilation, and renal replacement therapy respectively.<sup>24,25</sup> If these are not available, arrange for transfer to a specialised centre. Patients with substantial bleeding, worsening paralysis, dropping urine output, refractory shock, anaphylaxis non-responsive to adrenaline, or compartment syndrome may also require specialist management and intensive care.<sup>24</sup>

Having contact details of emergency transport and the referral centre readily available can avoid delays. Inform the receiving hospital about the patient's condition over the phone and send a referral letter with details of assessment and treatment.<sup>114</sup>

# What to cover on discharge and follow-up?

Patients who are clinically stable or asymptomatic with persistently negative 20WBCT after 24 hours may be discharged. Educate patients and their families on snakebite prevention and first aid, preferably using printed leaflets with clear visually represented information and minimal reliance on text.<sup>3 12</sup>

Inform patients who have received antivenom to report late adverse reactions. Arrange a follow-up after two weeks to review late reactions and sequelae.

### What are the long-term sequelae of snakebite?

There is insufficient data on long term sequelae after a snakebite.<sup>6</sup> Amputations following snakebite-related soft tissue injuries range from 5908 to 14 614 annually in sub-Saharan Africa, based on a meta-analysis of data published between 1970 and 2010.<sup>4</sup> Even in patients not requiring amputations, tissue loss may result in chronic ulcers, malignant transformation, and scarring.<sup>29</sup> Musculoskeletal sequelae such as contractures, wasting, and joint stiffness affected up to 3% of snakebite survivors in a study of 816 patients in Sri Lanka.<sup>115</sup> Cerebrovascular accidents result in persisting limb weakness and visual or cognitive impairment.<sup>29</sup> Eye exposure to venom can result in blindness.<sup>31</sup> Some patients with acute kidney injury may progress to chronic renal failure.<sup>116-120</sup> Limited data from case reports and observational studies from South Asia indicate that chronic hypopituitarism, a sequel of acute pituitary haemorrhage, can present as fatigue, arrested puberty, amenorrhoea, and hypothyroidism as late as 10 years after the bite.<sup>37 91 121 -123</sup> Snakebite survivors also have higher rates of post-traumatic stress disorder and depression compared with matched controls.<sup>57</sup> Ensuring access to physiotherapy, psychological services, and specialists, as needed, can be essential in managing long term sequelae of snake bite.

#### Areas for future research

- High-quality randomised controlled clinical trials evaluating the feasibility and effectiveness of pressure immobilisation in bites by different snake species
- Large, well designed clinical trials to establish safety, effectiveness, and optimal dose of antivenoms. The risks of anaphylaxis and sensitisation to animal proteins in antivenoms place ethical limitations on conventional phase I/II designs.<sup>124</sup> Some literature suggests that model based adaptive designs, as used to test anticancer drugs, could be safer alternatives for antivenom testing<sup>95</sup> 102 124
- Studies on envenoming syndromes to establish species-syndrome correlation and aid early identification of snake species
- Clinical trials to evaluate the effectiveness and safety of adjunctive treatment options including small molecular therapeutics such as secretory phospholipase A2 inhibitors (varespladib/varespladib-methyl), matrix metalloproteinase inhibitors (batimastat and marimastat), and peptide and oligomer based technologies such as toxin-specific monoclonal antibodies and aptamers<sup>125</sup> 126
- Observational studies with long post-discharge follow-up to determine the prevalence, severity, clinical progression, and risk factors of long term sequelae from snakebite

#### Additional resources

- Information on the spatial ecology of medically important venomous snakes, antivenom products, and the location of antivenom manufacturers by country or region can be obtained from the World Health Organization's Snakebite Information and Data Platform https://www.who.int/teams/control-of-neglected-tropical-diseases/snakebite-envenoming/snakebite-information-and-data-platform.
- Information on envenoming profiles of different snakes and their management can be obtained from the following sites:
  - African snakebites—WHO. Guidelines for the prevention and clinical management of snakebite in Africa. 2010. https://apps.who.int/iris/handle/10665/204458
  - South-East Asian snakebites—WHO. Guidelines for the management of snakebites. 2nd ed. 2016. https://apps.who.int/iris/handle/10665/249547

 Global snakes database—University of Adelaide. Clinical toxicology resources: Snakes. www.toxinology.com

#### **Education into practice**

- Think about the last time you treated a patient with snakebite. Reflect on the challenges you encountered while diagnosing and treating envenoming. What changes, if any, might you make to your approach next time?
- How do you review a snakebite patient as an outpatient discharge? Think about common persisting physical and psychological problems that you might have noticed during review. To what extent was the patient able to share difficulties in returning to routine life? How might you involve the patient in making decisions about long term?

#### How patients were involved in the creation of this article

No patients were involved in the creation of this article.

Contributors: RR formulated and wrote the initial draft. All authors searched the literature, framed manuscript content, contributed to critical revisions and approved of the final version. RR is the guarantor of this article.

The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. The authors are fully responsible for the contents and editorial decisions for this manuscript.

Competing interests: We have read and understood *BMJ* policy on declaration of interests and have no relevant interests to declare.

Provenance and peer review: Commissioned; externally peer reviewed.

We thank Abdulrazaq Habib, Bayero University, Kano, Nigeria; Colin J Forsyth, Drugs for Neglected Diseases initiative-North America; Ahmad Khaldun Ismail, Profesor Madya, Department of Emergency Medicine, Faculty of Medicine, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia; José María Gutiérrez, Instituto Clodomiro Picado, Facultad de Microbiología, Universidad de Costa Rica, Costa Rica; and Scott A Weinstein, Women's and Children's Hospital, North Adelaide, Australia for their instructive comments on this manuscript.

Supplementary illustrations on the pathophysiology of venom-toxin action were created with BioRender.com

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