

Antivenom, An Essential Underused Drug

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Abstract:

Antivenom has been the cornerstone of management for snake envenomation since its development and clinical use more than 100 years ago. Frequently used antivenoms are polyvalent antibodies, produced by immunizing animals. Like other protein drugs, antivenom has immunogenicity and may cause acute allergic reactions including ‘anaphylaxis’ ranging from mild to life threatening reactions. Premedication with subcutaneous adrenaline has clear benefit evidenced by reduction of number and extent of these events. Due to diversities of venom composition, to be maximally effective, antivenoms should ideally be produced by using the venoms from species of local origin.

For ensuring the ongoing safety and effectiveness of this antivenom, routine pharmacovigilance is necessary. Pharmacovigilance is a systematic, scientific study on adverse events that can be reported to concerned authority (Directorate General of Drug Administration (DGDA) in Bangladesh)

Introduction:

Snakebite envenomation is a time critical acute community emergency in the tropics. An estimated 5.4 million people worldwide are bitten by snakes each year with 1.8 to 2.7 million cases of envenoming. Around 81410 to 137880 people die each year because of snakebites, and around three times as many amputations and other permanent disabilities are caused by snakebites annually.¹

The estimated incidence of snakebite in rural Bangladesh is 623.4/100,000 person years (95% CI 513.4789.2/100,000 person years).² A recent survey conducted in 2022 across whole country by the Non-Communicable Diseases Control (NCDC) program,

by active or passive reporting. Introduction of pharmacovigilance will help to improve the monitoring and management of the AV related risks through identification and assessment of suspected drug adverse reactions, ineffectiveness, and other drug-related problems. Bangladesh drug regulatory authority (DGDA) encourages to report adverse events by health professionals following use of AV. At the same time need based distribution of AV and other logistics to the health care facilities across the country has to be established. Health authority should prioritize the need and take necessary actions to produce AV(s) using the venom from the locally collected medically important venomous snakes. Antivenom is an essential drug for managing a community emergency, snakebite envenomation.

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Directorate General of Health Services (DGHS), Government of Bangladesh (GOB) detected around 400,000 annual snakebite with 7500 deaths annually in Bangladesh (unpublished report).

The cornerstone of management for snake envenomation is antivenom, designated by the World Health Organization (WHO) as an essential medicine first time in 1977.^{3,4,5} The UN Sustainable Development Goal (SDG) 3.8 has clearly mentioned about ‘access to safe, effective, quality and affordable vaccines for all’ which is also a core component of Universal Health Coverage (UHC) (UN 2017).⁶ Antivenom consists of polyclonal antibodies (immunoglobulins) to several toxins present in snake venoms.^{7,8} They may be fractionated immunoglobulins like Fab or F(ab’)₂ or whole immunoglobulin (IgG) molecules.⁹ These antibodies are produced in animals, commonly horse, sheep, goats and rabbits, by repeated injection of small doses of snake venom. The polyclonal antivenom neutralize multiple toxins present in venom.^{9,10} While polyvalent antivenom is created by immunizing the host animal with the venom of multiple snake species,

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monovalent antivenom is developed against the venom of a single species of snake.¹⁰ In Bangladesh currently used antivenom contains antibodies against venoms of *Naja Naja*, *Bungarus Caeruleus*, *Daboia Russelii* and *Echis Carinatus*.

Different pharmacodynamic and pharmacokinetic properties of antivenom influence their motility, determining their ability to reach the tissue targets and their duration of action.⁹ Being animal protein they also have varying degrees of adverse reactions. The dose of antivenom, repetition of doses and the treatment regimen depend on molecular size and various other characteristics of the antivenom.

Antivenom must be administered as soon as possible to allow it to bind to venom (toxins) before the toxins spread to the target tissues and cause irreversible harm (such as pre-synaptic neurotoxicity, nephrotoxicity). Antivenom should be administered intravenously, as previous use of local or intramuscular administration detected delays in entry to the systemic circulation rapidly.¹¹

The administration of foreign proteins, most frequently equine, is the primary cause of hypersensitive reactions and other events, including pyrogenic reactions after antivenom treatment.^{12,13} Acute allergic reactions to antivenom are classified as mild, moderate and severe.¹⁴ Delayed reactions can occur and are referred to as serum sickness.^{15,16} However, a randomized controlled trial revealed that the reduction of immediate reaction to antivenom is possible with administration of adrenaline prior to antivenom.¹⁷

Clinical presentation and outcome of snakebite:

Snake venom can cause, besides local effects, a range of organ involvement like neurological (myasthenia like features leading to respiratory paralysis), coagulation derangement (leading to bleeding, shock, 'capillary leak syndrome' for example), acute kidney injury, cardiac manifestation. Survivors following envenomation may develop long term snakebite or treatment specific sequelae like amputation, chronic kidney disease, pituitary insufficiency, Post Traumatic Stress disorder.¹⁸

Bangladesh has 65 terrestrial venomous snake species and 16 species of sea snakes, so far listed and documented, of which medically important venomous species are 11.^{19,20} Bangladeshi patients following bite

by land snakes show 5 distinct syndromes of clinical features which can be broadly categorized in two groups of manifestations: dominant neurotoxicity by two species of cobra and five species of krait and haemato-renal toxicity by vipers; Russell's viper ('Chandrabora') and green pit viper (much lesser extent).

Pathogenesis of snake envenomation:

Snake venom comprises of a cocktail of more than two dozens of different proteins, mainly enzymes, non-enzymatic polypeptide toxins, and non-toxic proteins.^{21,22,23} Procoagulant enzymes in viperidae venom break down fibrinogen or activating prothrombin, factor V, X, and other clotting factors, which can lead to DIC, consumption coagulopathy, and incoagulable blood.

Neuro-myotoxicity is mostly due to Phospholipase A2.^{24,25} Polypeptide postsynaptic (á) neurotoxins reversibly bind to acetylcholine receptors at the motor endplate. Presynaptic (â) neurotoxins are phospholipases that irreversibly bind to pre-synaptic receptors and damage nerve endings.

Brief history of antivenom:

Albert Calmette, a French scientist is credited with producing the first snake antivenom against the snake *Naja naja* (Spectacled Cobra) 130 years before in 1894 at the Pasteur Institute in Lille, France.²⁵ With initial thoughts of generic use in all snakebites, soon it appeared that antivenom is specific to individual venom. The first horse-derived antivenom sera that he prepared were in clinical use in 1895 by Haffkine in India and by Lepinay in Viet Nam. The latter reported the first successful use of antivenin serum therapy in patients in 1896.²⁶

Subsequent initiatives to develop antivenom were made in several regions: in Brazil (1898), in Australia (1898), USA (1927), South Africa (1932), Costa Rica (1967). A polyvalent antivenom against the puff adder (*Bitis arietans*) and Cape cobra (*Naja nivea*) was first introduced in 1932.^{27,28,29} Venom research concentrates on immunological modification of venoms to reduce immunogenicity. Although venomology was first described in 2004 as a venom proteomics methodology,²⁷ the more recent definition encompasses the global study of the venom and the venom gland, incorporating characterization of the whole venom profile through

integration of proteomic, transcriptomic, and genomic methodologies.^{30,31,32}

Even with the cost-effectiveness of conventional antivenom manufacturing methods and significant advancements in antivenom quality, the antivenom crisis—the historical and present scarcity of commercial antivenom supplies in many parts of the Globe including Bangladesh—remains an unsolved problem.³³

Unfortunately, the pharmaceutical industry has generally shown little interest as AV is a low-profit product, as demonstrated by the 2014 discontinuation of production of Fav-Afrique® (Sanofi Pasteur), a polyvalent antivenom previously used to treat envenomation caused by medically relevant snake species of sub-Saharan Africa.³⁴

With the goal of lowering the morbidity and mortality from snakebite envenoming in the next seven years, the World Health Organization's (WHO) snakebite envenoming working group (SBE-WG) (with Dr. David J Williams and MA Faiz as Co-chair) recently unveiled a multi-component global strategy. It is envisioned that, this will encourage the necessary steps to ensure the availability and affordability of high-quality antivenoms in areas where they are desperately needed.³⁵

Role of antivenom in reduction of mortality:

In 2019, 2.94 million years of life lost (YLLs) (1.79 million - 3.74 million) and 63,400 deaths (95% uncertainty interval [UI] 38,900–78,600) worldwide were linked to snakebite envenoming. This translated into an age-standardized rate of 38 YLLs (ages 23 to 49) and 0.8 deaths (0.5 to 1.0) per 100,000. Globally, the age-standardized death rate and the number of young lives lost per 100,000 people fell by 36% (2–49) and 40% (6–55) between 1990 and 2019.³⁶ Though the death toll is not up to target of WHO but these significant changes occurred due to effective use of anti-venom. Locally in some of the tertiary care hospital in Bangladesh mortality after admission could be reduced to almost zero in some years.

How antivenom is developed:

Antivenom development undergoes along scientific process with standard protocol. Usually, venoms are collected from locally relevant medically important snakes with WHO standard venom collection, preservation and storage system.³⁷ Animals like horse,

sheep, goat are used for immunization with venoms. Plasma of the immunized animal is collected, and immunoglobulin purification done with standard procedure. With adjuvant, antivenom is produced for study. After animal study dose of antivenom, efficacy of antivenom need to be established. After preclinical and clinical assessment, marketing is done and post clinical survey started. The AV produced varies in efficacy and safety batchwise demanding a continued post-marketing surveillance of the product. Two varieties of antivenom are manufactured: liquid and lyophilized form, the later having long shelf life. The AV produced varies in efficacy and safety batchwise demanding a continued post-marketing surveillance of the product.

Adverse events of antivenom:

Being a product of animal serum AV, use is associated with adverse events which can be classified into acute reactions and delayed serum sickness.

Acute reactions:

Acute reaction can be mild like urticaria, nausea, vomiting, headache, fever to severe like 'anaphylaxis', hypotension, bronchospasm, cyanosis, altered level of consciousness.^{38,39,40,41}

In Sri Lanka, where only Indian manufactured polyvalent antivenoms are available, reported severe reaction rates were as high as 43%. It was found to be reduced by giving prophylactic subcutaneous adrenaline before administration of antivenom.^{42,43,44} In an early small size Bangladeshi study the incidence of adverse reaction using the Indian polyvalent AV was found to be upto 88.7% (31 out of 35) where pyrogenic reaction was more than 80%.⁴⁵ Despite such high rate of reaction they were successfully averted by medication and the outcome was found reasonably good.

The mechanism of acute allergic reaction to antivenom is not clear. It can be; i) type I hypersensitivity reaction mediated by IgE ii) anaphylactoid reaction mediated by complement activation iii) pyrogenic reaction due to presence of endotoxin. Type I hypersensitivity reactions are mediated by IgE antibodies reactive to specific antigens that are attached to basophil or mast cell Fc receptor which leads to release of histamine and other mediators causing increased vascular permeability, vasodilatation, bronchial and smooth muscle contraction, mucous secretion and local inflammation.^{46,47,48}

The presence of impurities in antivenom (heterologous animal protein) increases the possibility of 'anaphylactic shock' due to IgE antibodies especially among atopic individuals. Many laboratories are trying to reduce the impurities in antivenoms. The use of affinity and ionic exchange columns to purify the final product may be convenient and in fact, it has been proposed to improve its purity. Purification by chromatographic techniques alone has already been proposed.^{49,50}

Although antivenom reactions frequently happen in people who have never been exposed to horse proteins before, acute reactions may be the result of type I hypersensitivity. Complement activation can occur in antivenom due to presence of protein aggregates are originated mainly in immunoglobulin fraction during production. Complement activation, type I hypersensitivity, can occur in even highly purified antivenoms.⁵¹

Indian antivenom reactions were claimed to be not complement mediated and were possibly due to IG immunoglobulin complex and impurities in the antivenom.⁵² Several steps were taken to reduce the acute reactions like production of purer antivenom, giving with pre-medications, given as slow transfusion. Subcutaneous adrenaline has been found to be effective in reducing acute allergic reaction and is recommended in the National Guidelines of Bangladesh.⁵³ Hydrocortisone and antihistamine have no proven role in prevention of anaphylaxis.

Delayed serum sickness:

Serum sickness is a delayed hypersensitivity type of reaction due to IgG mediated immune response to the animal proteins in antivenom. It typically presents with fever, erythematous rash or urticaria and, myalgia, headache, nausea and vomiting, arthralgia, which may involve the temporomandibular joint, lymphadenopathy, periarticular swellings, mononeuritis multiplex, albuminuria and, rarely, encephalopathy. It may be started and persists between 5-20 days.^{54,55}

Prevention of adverse effect of antivenom:

Though several papers showed the preventive role of antihistamine and steroid (hydrocortisone), their result were not established in large scale studies, low dose subcutaneous adrenaline has role in reduction of allergic reaction following antivenom.¹³

Contraindication of antivenom:

There is no absolute contraindication to antivenom treatment in severely envenomed patients. However, atopic patients and those who have had reactions to equine antiserum on previous occasions have an increased risk of developing severe antivenom reactions. In such cases, antivenom should not be given unless there are definite signs of severe (potentially life-threatening) systemic envenoming. Pretreatment with adrenaline (epinephrine) 0.25/ ml of 0.01% solution subcutaneously followed by empirical histamine H₁-blocker and corticosteroid by intravenous injection is recommended (for established acute reaction). The patient should be closely observed for 3/ hours after antivenom has been given. Rapid desensitization is not recommended.⁵⁶

Physicians' concern regarding antivenom:

Physicians facing a case of snake envenomation often become worried about these acute adverse effects specially anaphylaxis. These have led to unjustified referral of the patients to higher health care facilities causing further delay in administration of antivenom. This delay has been proved to be fatal in many cases. Treating physician should have a clear understanding of the benefit and risk of using antivenom and should also be trained properly regarding administration of antivenom and management of possible adverse reaction. This should a part of undergraduate medical curriculum.

Need for pharmacovigilance (PV):

As antivenom contains animal derived antibody or antibody fragments, they can induce an acute hypersensitivity reaction. In a clinical trial based in Sri Lanka, 75% of participants had an acute reaction to antivenom, and 43% of these reactions were classified as severe.⁵⁷

PV is defined by the WHO as "the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problem". Currently, 194 countries are part of WHO and 131 countries are members of Program for International Drug Monitoring (PIDM) coordinated by the Uppsala Monitoring Center (UMC). WHO has recommended to establish public health strategies as an urgent measure to ensure the availability of AVs both safe, effective and affordable, especially for developing

countries as well as to improve the regulatory control over the manufacture, import and sale.

The aim of pharmacovigilance is to improve patient care and safety in relation to the use of medicines and all medical and paramedical interventions, improve public health and safety in relation to the use of medicines, contribute to the assessment of benefit, harm, effectiveness and risk of medicines, encouraging their safe, rational and more effective (including cost-effective) use, and promote understanding, education and clinical training in pharmacovigilance and its effective communication to the public. Health professionals are more likely to identify and report important ADRs if they have confidence in their ability to diagnose, manage and prevent such reactions. Both hospitalized and out-of-hospital patients have well-documented medication mistakes and adverse drug reactions (ADRs), which significantly increase morbidity and death. They are known to happen in community settings and also add to the quantity of hospital admissions. Many are avoidable and foreseeable.

Bangladesh currently does not produce AV, use the Indian AV, which ideally require independent tests for preclinical and clinical efficacy and clinical safety. Till such capacity is developed, introduction of pharmacovigilance will help to improve the management of the AV-related risks through the identification and assessment of suspected drug adverse reactions, ineffectiveness, and other drug-related problems. It is mandatory to ensure continuous safety and effectiveness of an affordable antivenom.⁵⁷

Events of anaphylaxis or adverse events following antivenom should be reported on regular basis, so that antivenoms can be compared. Bangladesh drug regulatory authority (DGDA) encourages to report adverse events by health professionals following use of AV. Anaphylaxis following antivenom can be defined according to National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network (NIAID-FAAN) consensus criteria and assessed severity using the Brown grading system.^{58, 59}

Fortunately, acute antivenom reaction is now much fewer following premedication with adrenaline and experts had urged for premedication as per the NGL through a position statement.⁶⁰

Academy of Allergy and Immunology criteria—which are identical to the NIAID-FAAN definition.⁶¹

NIAID-FAAN consensus criteria for defining anaphylaxis:⁶²

Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled:

- 1 Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula)

AND at least one of:

- a) Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
 - b) Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
- 2 Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
 - a) Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
 - b) Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
 - c) Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
 - d) Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
 - 3 Reduced BP after exposure to known allergen for that patient (minutes to several hours):
 - a) Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP
 - b) Adults: systolic BP of less than 90 mmHg or greater than 30% decrease from that person's baseline

Brown criteria for severity grading anaphylaxis¹⁴

- 1) Mild (skin and subcutaneous tissues only)
Generalized erythema, urticaria, periorbital oedema, or angioedema
- 2) Moderate (features suggesting respiratory, cardiovascular, or gastrointestinal involvement)

Dyspnoea, stridor, wheeze, nausea, vomiting, dizziness (presyncope), diaphoresis, chest or throat tightness, or abdominal pain

- 3) Severe (hypoxia, hypotension, or neurologic compromise) Cyanosis $SpO_2 \leq 92\%$ at any stage, hypotension (SBP < 90 mmHg in adults), confusion, collapse, LOC, or incontinence

Antivenom access: The procurement, distribution, storage in appropriate condition and use of AV is associated with inherent problem in the countries where snakebite is a public health problem particularly when the country do not manufacture AV.⁶³ The paucity of data of snakebite in the health services poses a problem of AV need identification which is often decided on 'wise-man approach' rather than on evidence. The procurement and supply sometimes do not match with need at the specific site which are rural hospitals, UZHC in Bangladesh. The AV has a shelf life, unless used the date will be expired. The physicians working in UZHCs in Bangladesh do not feel comfortable to use it even within shelf-life.^{64,65} The need for AV can be assessed by generating good snakebite data by a mandatory reporting of the event, at the same time a community and hospital-based surveillance system should be developed. A continuous supply of AV in strategic locations at least in upazila health complex (UZHC) close to the high-risk community is desirable. Deployment of AV by the NCDC, DGHS, GOB through a tier specific strategy and stockpile at district level, and use of AV in several upazila hospitals following envenomation in recent days is encouraging. More works are needed to ensure availability of AV 24/7 for envenomed patients in different tiers. Other ancillary support system and logistics relevant for management is essential so also availability of skilled team of health professionals is crucial. For managing envenomation, a number of generic and specific skills are needed which are expected to be achieved during pre-service education and can be developed further during case management. Revisiting the curriculum for providing teaching on community emergencylike snakebite is urgently needed including teaching on antivenom in the pharmacology session in the education of health care professionals' students.

The snake venom has specificity to species and specificity also varies with geographical range found more than on hundred years before, thus recommended

by WHO to have country specific AV. Bangladesh is yet to have country specific AV which is a long overdue. The very early initiative taken by the NCDC, DGHS, GOB to generate basic country specific venom data by setting up a Venom Research Centre (VRC) is a noble initiative, much appreciated.

A widespread recent press coverage of the emergence of Russell's viper ('Chandrabora'/'Ulo bora') with reporting of the snake from 27 districts of Bangladesh (Data from VRC, Bangladesh) created lots of chaos, confusion but at the same time awareness and enthusiasm among the public and the Government which should be converted into priority public health action for having country specific antivenom. Bangladesh can think of continuation of procurement and use of imported polyvalent AV, at the same time focus on development of one local 'bivalent' AV for 'haematotoxic' snakes (for Russell's viper and Green pit viper) and another polyvalent AV for neurotoxic snakes like cobras and kraits on a fast track initiative in order to achieve the WHO target of reducing the mortality and disability by 50% by 2030. In addition, active community engagement for appropriate first aid and prevention of bite along with early treatment seeking to nearest upazila/district hospital are critically important.

Conclusion:

Antivenom, antibodies to snake venom, despite being developed century ago and used since then, is still an underutilized lifesaving medication. Proper knowledge, attitude and skill among physician regarding use of antivenom and management of adverse reaction may overcome the situation and ensure proper and timely administration of AV thus saving many more lives. Development of antivenom specific to local snake venoms should be a priority. The supply chain of antivenom should be developed and established on a need-based priority. Committed political and administrative initiatives are required to improve the snakebite situation in Bangladesh to meet SDG goal.

Conflict of interest:

We have no conflict of interest to declare

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