Section 18

Poisoning and Toxicology

223. Management of Organophosphorus Poisoning
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224. Snakebite
   Sanjib Kumar Sharma

225. Snakebite in Indian Scenario and Its Management
   Vinay Rampal
Abstract
Poisoning both accidental and intentional is a single contributor to mortality and morbidity throughout the world. The commonest cause of poisoning in developing countries including India is pesticide, the reason being agriculture based economics and organophosphorus (OP) constitute the largest bulk of pesticides. Clinical manifestations result from inhibition of acetylcholinesterase and stimulation of muscarinic and nicotinic receptors and characterized by pinpoint pupil, excessive salivation and sweating, bronchospasm leading to respiratory distress, CNS, and neuromuscular dysfunction. After initial stabilization, atropine should be used in appropriate doses and ventilator support may be required for those who developed respiratory failure due to neuromuscular dysfunction.

Introduction
Poisoning both accidental and intentional is a single contributor to mortality and morbidity throughout the world. The most common cause of poisoning in developing countries including India is pesticide; the reason being agriculture based economics and organophosphorus (OP) constitute the largest bulk of pesticides. According to recent WHO data, it is estimated that deliberate ingestion of pesticides causes 370,000 deaths every year (https://www.who.int/ipcs/poisons/en/). However, these figures are probably an underestimate, especially in developing countries because of insufficient regulatory and surveillance systems, shortage of trained medical manpower, and ineffective utilization of existing facilities. India is a country with about 60–70% rural population, and agriculture is a major component of the economy. Every year, there are about 10,000 reported cases of pesticide poisoning in India with a mortality rate varies between 15% and 30% and is the fourth most common cause of mortality, especially in rural areas. The National Poisons Information Center (NPIC) was established at All India Institute of Medical Sciences, New Delhi, in 1995 to provide toxicological information and advice on the management of poisoned patients across the country. A survey done by NPIC from 1999 to 2002 reported a total of 2,719 poisoning, of which agricultural pesticides represent 12.8% of total cases. On further analysis of the main data, it was found that OP poisoning represents 18.75% cases of all agricultural products.

Pathophysiology
Organophosphorus compounds (OPCs) inhibit the function of acetylcholinesterase (AChE) by binding into the acyl pocket at the active site of AChE. The binding of a phosphate group to the serine amino acid at the active site of AChE changes the configuration of the enzyme molecule and make it dysfunctional. Normally the cholinesterase rapidly hydrolyzes the neurotransmitter acetylcholine into inactive fragments of choline and acetic acid. The neurotransmitter acetylcholine is present in the terminal endings of all postganglionic parasympathetic nerves, at myoneural junction, and at both parasympathetic and
sympathetic ganglia. The inhibition of cholinesterase leads to accumulation of acetylcholine at synapses, causing overstimulation and subsequent disruption of transmission in both central and peripheral nervous system.

**Clinical Features**

Patients with OP poisoning can become symptomatic within minutes depending on the route and degree of exposure. Most victims become symptomatic within 8 hours of exposure and virtually all within 24 hours. The clinical manifestations can be classified into: cholinergic crisis (muscarinic or nicotinic receptors) (Table 1), CNS effects, and sequelae (Intermediate syndrome).

**Intermediate Syndrome**

Approximately 10–40% of OP poisoning develop intermediate syndrome which typically manifests after 24–96 hours of exposure. It was first described as type II paralysis. It reflects excessive cholinergic stimulation of nicotinic receptors and is characterized by respiratory and bulbar symptoms as well as proximal muscle weakness, diminished deep tendon reflexes, and respiratory failure. The sensory system remains intake and full recovery is evident in 4–18 days. This syndrome almost never found with carbamate poisoning.

**Diagnosis**

Diagnosis of OP poisoning is based on the history of exposure to a known OP compound and classic clinical feature like miosis. Two mnemonics which help to remember the clinical manifestations are: DUMBELS: Diarrhea, Urinary frequency, Miosis, Bronchospasm, Emetics, Lachrymation, Salivation; SLUDGE and the Killer Bees: Salivation, Lachrymation, Urinary frequency, Diarrhoea, Gastric distress, Emetics and Bronchospasm, Bronchorrhea, and Bradycardia. For nicotinic effects, think of the days of the week: Monday = Mydriasis, Tuesday = Tachycardia, Wednesday = Weakness, Thursday = Hypertension, Friday = Fasciculation.

Estimation of butyrylcholinesterase activity in plasma (or AChE in whole blood) helps in confirming the diagnosis. However, their importance is limited only for clinical research due to unavailability issues and drawback (use and interpretation). Studies showed that RBC-AChE is a good marker of neuronal function, severity of poisoning, and the need for atropine in patients with OP poisoning, especially initial low plasma/RBC-AChE and high glucose level are good marker for predicting OP induced intermediate syndrome. However, one should not wait for the report to come before starting treatment as normal value of the enzyme does not exclude the diagnosis of OP poisoning.

An atropine challenge test may sometime help in diagnosing OP or carbamate poisoning where history is insufficient to suggest exposure but patients present with findings suggestive of cholinergic poisoning. A test dose of 1–5 mg of atropine (0.05 mg/kg in children) should produce classic antimuscarinic effects like mydriasis, tachycardia, and dry mucus membrane. In contrast, the persistence of cholinergic findings after an atropine challenge strongly suggests OP or carbamate poisoning.

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**Table 1** Clinical manifestations of organophosphorus (OP) poisoning

<table>
<thead>
<tr>
<th>Muscarinic effects</th>
<th>Nicotinic effects</th>
<th>CNS effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miosis</td>
<td>Muscle fasciculations</td>
<td>Unconsciousness</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>Paralysis</td>
<td>Confusion</td>
</tr>
<tr>
<td>Nausea</td>
<td>Pallor</td>
<td>Toxic psychosis</td>
</tr>
<tr>
<td>Vomiting</td>
<td>Muscle weakness</td>
<td>Seizures</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Hypertension</td>
<td>Fatigue</td>
</tr>
<tr>
<td>Salivation</td>
<td>Tachycardia</td>
<td>Respiratory depression</td>
</tr>
<tr>
<td>Lachration</td>
<td>Mydriasis (rare)</td>
<td>Dysarthria</td>
</tr>
<tr>
<td>Bradycardia</td>
<td></td>
<td>Ataxia</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td></td>
<td>Anxiety</td>
</tr>
<tr>
<td>Diaphoresis</td>
<td></td>
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<tr>
<td>Wheezing</td>
<td></td>
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<tr>
<td>Urinary incontinence</td>
<td></td>
<td></td>
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<tr>
<td>Fecal incontinence</td>
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</tr>
</tbody>
</table>

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Other ancillary investigations that may help in diagnosis are: leukocytosis, high hematocrit, hyper- or hypoglycemia, anion gap acidosis, and increased serum creatine kinase.

**Management**

Treatment goals include support of vital signs, preventing the further absorption of the poison (decontamination), administration of specific antidotes, and prevention of re-exposure.

**Supportive Measures**

- **Check ABC**: Make sure that patient has a patent airway and adequate breathing and circulation. Provide high-flow oxygen with mask. Intubate the patient in compromised airway or breathing.
- **Position of the patient**: Patient should be kept in the left lateral position, preferably with head down position, to reduce risk of aspiration of stomach contents.
- **Frequent suctioning is essential as excessive oropharyngeal and respiratory secretion may occlude the airways.**
- **Obtain intravenous (IV) access and give IV fluid (0.9% NS) to replace loss. Aim is to keep the systolic blood pressure above 80 mm Hg and urine output above 0.5 mL/kg/hr.**
- **Record pulse rate, blood pressure, size of pupil, presence of sweat, and findings of chest on auscultation at the time of first atropine dose. Prepare atropine chart.**
- **Continuous monitoring of respiratory function. If tidal volume is less than 5 mL/kg or vital capacity is less than 15 mL/kg, or if they have apneic spells, or PaO₂ < 60 mm Hg on FiO₂ > 60% immediately intubate and ventilate the patient.**
- **It is important to assess flexor neck strength regularly in conscious patients by asking them to lift their head off the bed and hold it in that position while pressure is applied to their forehead. Any sign of weakness is a sign that the patient is at risk of developing intermediate syndrome.**
- **The following drugs are contraindicated: Parasympathomimetic, phenothiazine, antihistamine, and opiates. One should not administer Succinylcholine to ventilated patient.**
- **Treat agitation by reviewing the dose of atropine being given and provide adequate sedation with diazepam. Physical restraint of agitated patients in warm conditions risks severe hyperthermia, which is exacerbated by atropine because it inhibits normal thermoregulatory responses, including sweating. Adequate sedation is therefore important.**
- **If metabolic acidosis persists despite correction of hypoxia and adequate fluid resuscitation, consider correction with IV bicarbonate guided with arterial blood gas analysis.**
- **Broad spectrum antibiotics may be required to prevent secondary infection.**

**External and Gastric Decontamination**

Decontamination may be done by removing the contaminated clothes and washing with soap and water. Although there are no evidence based studies; however, this seems to be cost effective and an easy to perform practice by which we can reduce further absorption of the poison into the system. Gastric lavage is a widely used decontamination procedure globally despite the absence of confirmed benefit by randomized controlled trials (RCTs). OP compounds are easily absorbed through mucus membrane and gastric lavage may play a role in the first hour of poisoning. It may be performed, in a patient who is awake, preferably in the left lateral position with tap water (5–10 mL/kg). However, the duration for which the OP compounds remain in the stomach is still unknown and there are concerns for increased risk for aspiration pneumonia and respiratory distress. Activated charcoal has been widely used for absorbing pesticide poisons. The two commonly used regimens of activated charcoal are:

- **Single dose of 50 mg**
- **Multiple doses of 25 mg.**

However, no RCT has addressed this issue, especially in OP poisoning.

**Antidotes**

The three most commonly used classes of antidotes are: Atropine, Oxime (Pralidoxime), and Benzodiazepine.

**Atropine**: Atropine is an antagonist to muscarinic receptors of Acetylcholine and is the mainstay of treatment of acute OP poisoning. It is used to reverse the cholinergic effect and has no role in neuromuscular junction and
muscular weakness. The five markers indicating atropine requirements are:

- Miosis
- Excessive sweating
- Bronchorrhea and bronchospasm causing difficulty in air entry
- Bradycardia
- Hypotension.

The two commonly used regimens are:

- Bolus dose administration
- Incremental dose administration with rapid escalation.

The aim of therapy is to prevent bradycardia, maintain blood pressure, clear lungs, and dry skin. Bolus dose is defined as 2–5 mg of atropine every 10–15 minutes followed by maintenance using reduced dose or increasing the time interval between the doses. Incremental dose is defined as 1.8–3 mg of atropine by intravenous infusion, repeating the doses every 5 minutes interval, then doubling the doses each time until atropinization occurs, followed by 10–20% of atropine required for atropinization to be given every hour by intravenous infusion. The end points of atropinization are:

- Clear chest on auscultation with resolution of bronchorrhea
- Heart rate of more than 80/minute
- Systolic blood pressure of more than 80 mm Hg
- Dry axillae
- Pupils of more than 2 mm.

Once atroponized, these five parameters should be monitored every 15 minutes initially which can be gradually increased to 1-2-3 hours depending on the state of atropinization (Table 2). Atropine is associated with toxic effects like confusion, agitation, various arrhythmias like multiple ventricular ectopics, atrial arrhythmia, A-V dissociation, raised intraocular pressure, hyperthermia, hallucination, and delirium and ileus. Once atropony starts, it should be immediately stopped. It may be restarted at 70–80% of the previous rate once the patient settles down. Duration of atropine therapy depends on the severity and response to therapy; usually it is maintained for 24–48 hours and gradually withdrawn over 3–5 days.

**Oximes:** Oximes reactivate acetylcholinesterase by removing the phosphate moiety from the acetyl pocket. In addition, they also slow the ageing of the phosphorylated enzyme complex and have a direct action in converting OP to a harmless compound. They are effective in counteracting both the muscarinic and nicotinic effects. Pralidoxime (2-PAM) is the only oxime available in India. Despite clear reactivation of red cell AChE, current evidence is insufficient to indicate whether oximes are harmful or beneficial in the management of acute OP poisoning. The WHO recommends a regimen of 30 mg/kg body weight bolus infusion followed by 8 mg/kg body weight/hour intravenous infusion of PAM to all symptomatic patients who need atropine. Pralidoxime is expensive and not free from toxicities. In a recent RCT from India which included 200 patients with moderate OP poisoning stated that high-dose pralidoxime iodide (2 g loading dose, followed by 1 g either every hour or every 4 hours for 48 hours, then 1 g every 4 hours until recovery) associated with reduced case fatality, fewer cases of pneumonia, and reduced time on mechanical ventilation. A Cochrane review including two RCTs reported no clear evidence of benefit or harm from pralidoxime in
OP poisoning. Few other meta-analyses combined non-randomized or historically controlled observational studies with RCTs concluded that oximes are harmful.

**Benzodiazepine:** Patients with OP poisoning are often developed agitated delirium due to multiple reasons, viz. atropine toxicity, pesticide itself, brain hypoxia, alcohol ingested along with the poison, and medical complications. Diazepam (5–10 mg IV slowly, every 15 minutes, up to a maximum of 30 mg and for children 0.25 mg/kg IV slowly, every 5–10 minutes, up to a maximum 10 mg) is easily available and best drug to control agitation. It also helps in sedation in ventilated patient and used as first-line drug for convulsion which although rare but may occur especially with organophosphorus nerve agents (such as sarin, soman, and tabun). However, there are no trials evaluating the efficacy of benzodiazepine as a primary treatment for OP poisoning.

**Newer Therapies**

**Magnesium sulfate:** Intravenous magnesium sulfate (MgSO₄) has a role in the management of acute OP poisoning as it blocks the voltage gated calcium channel, thereby reducing the release of acetylcholine from synapses. It also reduces the NMDA receptors mediated CNS activation. Intravenous MgSO₄ (4 g) on first day has shown to decrease hospitalization period and improve outcome.

**Clonidine:** Clonidine, an alpha-2 receptor agonist, inhibits the release of presynaptic acetylcholine and thereby decreases the cholinergic symptoms. Optimum dose of clonidine regimen is bolus injection of 0.15–0.30 mg followed by infusion rates of 0.5 mg/24 hours.

**Alkalization:** Alkalization by sodium bicarbonate (blood pH between 7.45 and 7.55) may help in OP poisoning as shown by some studies.

**Fresh frozen plasma (FFP):** FFP is a cellular component of blood containing clotting factors, proteins, and many enzymes. It is hypothesized that the enzyme butyrylcholinesterase presents in FFP will sequester the free poison present in blood and remove them from circulation.

Removal of OP from blood by using hemodialysis, hemofiltration, or hemoperfusion is not yet clear. However, in a recent report, it was claimed that hemofiltration after dichlorvos poisoning had revealed beneficial therapeutic effect.

**Prevention of Re-exposure**

Once the patient is fully recovered, he should not be re-exposed again to OPCs for at least few weeks. It has been said that risk for serious harm can happened on re-exposure to a previously harmless product because of alteration in body chemistry of the host due to previous poisoning. In ideal condition and if facility available, following acute poisoning patient should be precluded from further exposure to OPCs until sequential cholinesterase level is available and confirm that cholinesterase level reached a plateau phase. Plateau phase is defined when sequential determination does not differ by more than 10% and it normally takes 3–4 months following acute poisoning. It is important to note that optimization of health education system amongst the agricultural workers regarding procedure of pesticide handling, strictly following the operative and well-maintained spraying equipment and using necessary precautions at all stages of pesticide handling are essential for reducing their exposure to pesticides.

**Conclusion**

Being cheap and easily available over the counter, OP poisoning is becoming a major health problem, especially in a developing country like India. Acute OP poisoning is a medical emergency leading to severe toxicity and death. It can be diagnosed on the basis of history of exposure to OP compounds and clinical examination. The estimation of RBC AChE can have a role for confirmation of diagnosis. Early initiation of selective decontamination and antidote therapy (particularly atropine) with close monitoring for complications are important in preventing death due to OP poisoning.

**References**

Abstract
Snakebite is the second deadliest neglected tropical disease. Southeast Asia is the most affected region in the world. Manifestation of envenomation can be either neurotoxic and/or hematotoxic depending upon biting species. Local manifestation can be severe depending upon the species involved in envenomation. In absence of specific definitive diagnostic test, clinical features along with circumstance of bite may help identifying biting species of snake. Snakebite with systemic envenomation is life threatening medical condition and timely administration of antivenom along with supportive therapy can save life. Administration of antivenom can be associated with antivenom reactions including life threatening anaphylaxis. Prophylaxis administration of subcutaneous adrenalin can reduce the incidence of severe adverse reaction related to antivenom.

Introduction
Snake bite is a public health issue with acute and chronic consequences. It mostly affects economically disadvantage population of rural communities in the tropics. South Asia, due to its high human and snake population and agricultural activities, is the world’s most affected region. Most of the victims of snakebite die (97% in India and 80% in Nepal) before reaching treatment centers leading to serious misreporting. Community based study has shown that the snakebite figures are alarming.

Snakebite is a life threatening medical emergency. Survival of the victims depends much on immediate transportation of the victim to the nearest health-care center where antivenom can be administered and supportive therapy is available.

Burden and Characteristics of Snakebite
Around the globe snakebite occurs in approximately 5 million people. It is estimated that snakebite causes up to 138,000 deaths and 400,000 disabilities. The Southeast Asia Region has one of the highest snakebite burdens in the world and 70% of all global snakebite deaths occur in South Asia. In India, the direct estimate of deaths attributable to snakebite in 2005 was 46,000 (99% CI 41,000–51,000), or 1 snakebite death for every 2 HIV/AIDS deaths.

The characteristics of snakebite in South Asia are shown in Table 1.

Medically Important Venomous Snake of India and Nepal
There are around 300 species of snake found south of the Himalayas. Among them approximately 67 are front fanged venomous species. Medically the most important venomous snakes, also known as “BIG FOUR” are Russell’s viper (Daboia russelii), Common cobra (Naja naja), Common krait (Bungarus caeruleus), and Saw scaled viper (Echis carinatus). The pit viper species; Malabar (Trimeresurus malabaricus), Green pit viper (Trimeresurus albolabris), Hump-nosed viper (Hypnale
hypnale), Bamboo pit viper (Trimeresurus stejnegeri); Sea snakes (Hydrophiinae) and others like the King cobra (Ophiophagus hannah), Monocle cobra (Naja kaouthia), Banded krait (Bungarus fasciatus), Sind krait (Bungarus sindanus), and Echis sochureki are important causes in certain geographical areas.

**Clinical Manifestation**

Snakebite is a life-threatening medical emergency. Prompt identification of early signs of systemic envenoming is crucial for the optimal management of the victims. Snakebite may have one of the following consequences:

- **Dry bite**—It may be due to bite from non-venomous snake or bite by venomous snake without envenoming. Fang mark (bite mark) may be present.
- **Local effects of venom** in parts of bitten site like swelling, bullae formation, necrosis, etc. This may extend to whole limb in viper bite. Secondary infection may lead to abscess formation.
- **Absorption of the venom** in systemic circulation leading to systemic manifestation. Depending on the biting species the systemic manifestations are neurotoxicity or hematotoxicity.
- **Effects of traditional treatment**, for example, local gangrene due to tight tourniquet, pain abdomen, vomiting, etc. due to congestion of chilies, herbal medicine, etc. Tight tourniquet/s may cause manifestations that may be confused with local envenoming.
- **General manifestation with or without snake envenoming** may result in excessive fear, nausea, vomiting, malaise, pain abdomen, weakness, prostration, excessive salivation, etc.

**Elapidae Groups of Snakes (Neurotoxic Features)**

Elapidae groups of snakes envenoming produce descending paralysis due to neuromuscular blockade. The important neurotoxic features are: Ptosis, diplopia, ophthalmoplegia, pupillary dilatation, inability (or limitation) to open mouth and/or tongue extrusion, inability to swallow, broken neck sign (patients cannot hold his/her neck straight when sitting up from supine position), skeletal muscle weakness, loss of gag reflex, paradoxical breathing (outward protrusion of abdomen during deep inspiration), and respiratory failure. Paralysis of tongue and muscle of deglutition may lead to upper airway obstruction. This may lead to asphyxia due to aspiration of pooled secretions. Hypoxia-associated manifestation like cyanosis and hypoxic brain injury may be secondary to respiratory failure. Abdominal pain may suggest krait envenoming in appropriate circumstance and is likely due to venom induced submucosal hemorrhages in the stomach.

**Viperidae Group of Snakes (Hematotoxic and Cytotoxic Features)**

Venom of Russell’s viper and saw scaled viper manifest as systemic bleeding. Feature of neurotoxicity may also present as added manifestation. Systemic manifestation of coagulopathy can also present in green pit viper envenoming. Malabar pit viper is attributed to cause significant morbidity in India.

Spontaneous bleeding from various orifices and mucosal surface is the major manifestation of viper envenoming. The bleeding is common from venipuncture...
site, gums, nose (epistaxis), respiratory system (hemoptysis), gastrointestinal system (melaena, rectal bleeding), genitourinary system (hematuria, bleeding from vagina), bleeding into the mucosae (subconjunctival hemorrhage), skin (petechiae, purpura, ecchymosis), retina (bleeding into tears), bleeding from inflicted wound, if any, bleeding into internal organs like brain and intracranium, lungs or abdomen, acute kidney injury and other organ dysfunction may occur secondary to hypotension following bleeding. Laboratory evaluation reveals prolonged bleeding time (BT) and clotting time (CT), increased prothrombin time and INR. Twenty-minute whole blood clotting test (20 WBCT) is useful bedside test to see incoagulability of the blood and can detect venom induced coagulopathy.

**Rhabdomyolysis**

Rhabdomyolysis is characterized by muscle pain, and muscle necrosis that releases intracellular muscle constituents into the circulation. Creatine kinase level is highly elevated. Myoglobinuria may be present. All myotoxic snake venoms contain phospholipase A2, which is responsible for the rhabdomyolysis. Russell’s viper, saw scaled viper, hump-nosed pit viper, green pit viper, and sea-snake can produce rhabdomyolysis (Table 2).

**Long-term sequelae of snakebite:** Long-term effects of snake bite may occur. Some known sequelae are as follows:

- Chronic ulceration, bone infection (osteomyelitis) or arthritis
- Physical disability

- Chronic kidney disease due to bilateral renal cortical necrosis and chronic panhypopituitarism may occur in Russell’s viper envenoming
- Sequelae of intracranial bleeding in hematotoxic envenoming
- Delayed psychological morbidity like depression and anxiety, impaired functioning, post-traumatic stress disorder, and unexplained residual physical disability as reported from Sri Lanka.

**Diagnostic Test for Snakebite Envenoming**

**Neurotoxic Envenoming**

Neurotoxic envenoming is clinical diagnosis and laboratory investigations is rarely of help.

**Hematotoxic Envenoming Due to Vipers**

- Prolonged BT and CT
- Increased INR
- Incoagulable blood as demonstrated by 20 WBCT (positive 20 WBCT)
- Raised urea and creatinine, if AKI develops
- Leukocytosis indicates systemic envenoming. Hemoconcentration may occur due to systemic bleeding and platelet count may decrease in case of viper envenoming.

**Management of snakebite:** Management of snakebite involves the following steps:

- First aid and transportation to the hospital
- Immediate clinical assessment and resuscitation

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**TABLE 2** Summary of the clinical feature of snakebite

<table>
<thead>
<tr>
<th>Feature</th>
<th>Cobra</th>
<th>Krait</th>
<th>Russell’s viper</th>
<th>Saw-scaled viper</th>
<th>Humped nose viper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local pain/Tissue damage</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Neurological signs</td>
<td>Yes</td>
<td>Yes</td>
<td>No*</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Coagulation abnormality</td>
<td>No</td>
<td>No**</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
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<tr>
<td>Response to neostigmine</td>
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<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Response to antivenom</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

* May be seen as added feature to hemostatic abnormality
** May be seen in envenoming with *Bungarus niger* (Greater black krait)
* May be seen in envenoming with *Bungarus caeruleus* (common krait) other than common krait (*Bungarus caeruleus*)
Poisoning and Toxicology

**Antivenom treatment**

**Supportive/Ancillary treatment**

**Treatment of the bitten part**

**First aid and transport to the hospital:** The most of the envenomed patient of our region die before reaching hospital and this is likely due to delay in transport of victim in snakebite causing neuroparalysis. So all means should be applied to transport the patients, as soon as possible, to the hospital or snakebite treatment center, where facilities to administer antivenom exist.

The recommended first aid methods are:
- Reassurance.
- Immobilization of the bitten limb using a splint or sling. Time should not, however, wasted searching for this materials and delay transport of the patient.
- Tight fitting ornaments and clothing should be removed. Do not inflict cutting, sucking, electrocautery, etc. of the bite wound.
- Rapid transport: Transportation of the victims to the nearest health center with facility to treat snake envenoming at soonest possible. Transport using motorcycle is found to save life in snakebite envenoming. The victim is seated and held between driver and pillion rider.
- Tight (arterial) tourniquet must be discouraged.

**Rapid clinical assessment and resuscitation:** Snakebite is a medical emergency. A quick clinical assessment to decide whether patient needs antivenom therapy and/or resuscitation should be done upon arrival of the victim. Clinical conditions when snakebite victim may require urgent resuscitation are:
- Hypotension and shock
- Respiratory distress and respiratory failure
- Cardiac arrest
- Rapid deterioration or development of features of severe envenoming

**Antivenom therapy:** Antivenom is the only specific treatment from snakebite envenoming. Effective against the four common species of snakes found in India; Russell’s viper (*Daboia russelii*), Common cobra (*Naja naja*), Common krait (*Bungarus caeruleus*), and Saw scaled viper (*Echis carinatus*). Antivenom currently is unlikely to be effective against similar sounding species of snakes.

### Indications for Antivenom

- Presence of definite evidence of neurotoxicity. Ptosis is the earliest reliable sign of neurotoxicity.
- Evidence of coagulopathy: Abnormal (positive) 20WBT, spontaneous systemic bleeding (gums, hemoglobinuria, myoglobinuria, and mucosa, bleeding).
- Rapid extension of local swelling (more than half of limb) which is not due to pit viper bite or tight tourniquet application.
- Cardiovascular collapse, i.e., shock and hypotension.

### Dose of Antivenom

Amount of injected venom during snakebite is similar for children and adults. Therefore, the dose of antivenom for children is same as adult dose.

**Initial dose:** Neurotoxic/hematotoxic envenoming: 10 vials (100 mL) is further diluted or mixed with dextrose water or saline (100–400 mL). Then it is administered with intravenous infusion at the rate of 2 mL/min (40–60 min at 60–70 drops/min).

When to repeat the dose of antivenom?

- **Neurotoxic envenoming:** If neurological sign/s deteriorates an IV push of 5 vials of antivenom (50 mL reconstituted antivenom) should be administer at 2 mL/min.

- **Hematotoxic envenoming:** Repeat 20WBCT (or other test for coagulation) after 6 hours. If 20WBCT is abnormal (uncoagulable blood) or other coagulation test are abnormal repeat 5 vials of antivenom (50 mL reconstituted antivenom) IV push at 2 mL/min. This can be repeated every 6 hours till coagulation profile is corrected.

**Note:** Do not use antivenom more than 20 vials or so. Administration of higher dose antivenom is unlikely to be useful, if patient has not responded to initial bolus or around 20 vials of antivenom.

### Prevention of ASV Reaction

Prophylactic subcutaneous adrenalin (epinephrine) should be routinely administered before initiation of antivenom treatment to prevent antivenom reaction. However, it should be avoided in older patients with evidence or suspicion of underlying ischemic heart
Antivenom reaction: Three types of antivenom reaction can occur.

- **Anaphylaxis:** It usually develops within 3 hours of antivenom initiation. Common features are itching, which may be intense, urticaria, fever, angioedema, dyspnea due to bronchospasm, laryngeal edema, hypotension, etc. Intramuscular adrenalin must be given at first sight of sign of anaphylaxis. Details of treatment of anaphylaxis related to snakebite can be found in national guideline of snakebite management of Nepal and India.

- **Pyrogenic reaction:** Usually develops 1–2 hours after treatment initiation. Features include, chills, rigors, fever, fall of blood pressure, and febrile convulsion may develop in children.

- **Late reaction (serum sickness type):** It can developed 1–12 (mean 7) days after receiving antivenom. Features include fever, itching recurrent urticaria, arthralgia, myalgia, lymphadenopathy, proteinuria, etc.

Supportive therapy: Antivenom treatment alone cannot always prevent respiratory paralysis. Patients with impending respiratory failure artificially ventilated to avoid asphyxiation and hypoxia. Similarily, appropriate measure to be taken to treat hypotension and shock. Patients with acute kidney injury may need dialysis therapy, if indicated. All snakebite patients should receive tetanus toxoid injection at the time of discharge. Neostigmine or may be administer along with atropine, if antivenom is not available for weakness or paralysis secondary to envenomation by a snake capable of causing postsynaptic neurotoxicity. Local wound should be care as like other wound and secondary infection should be treated accordingly.

### Conclusion

Snakebite is a true neglected tropical disease that mostly affects the most impoverished people of remote rural area. Immediate transport to health center and timely administration of antivenom, when indicated, along with supportive therapy are key to survival. Local envenomation may need prolonged wound care. Reaction to antivenom, which can be severe, can be reduced by subcutaneous adrenalin prior to antivenom infusion.

## Suggested Readings

Abstract

We Indians take pride in Worshipping Vasuki Naag, who being instrumental in Churning of sea for Nectar between the gods and the demons, and, Bhujang who adorns the head of lord Shiva still, the mere imagination of a bite by the smallest of kraits causes perspiration in strongest of human beings. We also take pride in calling ourselves the biggest democracy in the world offering free medical aid to all. Today, when we are thinking of landing at Mars, every year, hundreds of thousands of poor farmers, construction workers, forest employees, trekkers, and migrant laborers lose their precious lives, which can be easily saved by proper timely intervention. Snakes rightly called the sons of soil are as much part of the universe as human beings and created to rid the universe of smaller nuances like rodents and other creepers should be properly taken care of by taking proper precautions with dwellings, footwear, gloves use of stick and light while going to old ruins, fields, forests, and night roaming, especially during summer and monsoons, when the snakes move freely around in tall grass and during floods. Even if bitten, all types of venomous snakebites are amenable to treatment and the hub of treatment the polyvalent anti venin serum (AVS) is available free of cost in all the dispensaries/health centers but what is needed is education and awareness of the populace and the relief givers. In the following pages an effort is being made to bring forth the lessons learnt during last 35 years of treating more than 8,000 snakebite cases, especially the deadliest ones from Kandi area (dry belt of Shivalik Hills).

Introduction

Although snakes constitute an alma-mater of all medical emblems the staff of Aesculapius (Fig. 1) and the staff of Appolo, the Cadeceus (Fig. 2) still they continue to remain an enigma for not only the human society but the medical profession as well, when it comes to the management of snakebite poisoning. They (snakes) not only find a mention in the Hindu religious books, wherein they are worshipped for attainment of love, health, procreation, wisdom & virtue as “Bhujang” adorning the head of Lord Shiva and “Vasuki” being credited with churning of Ocean for Nectar (Amrit). On the contrary in the Christian mythology, they are treated as backbiters needing pithing. In the developing world most snakebites occur in those who work or sleep outside, such as foresters, farmers, hunters, fishermen, herdsmen, the Army personnel, the trekkers, and the migrant laborers, while in the United States & the Europe, those keeping them as pets are bitten as the famous Aspi of Cloepetra (Fig. 3). Snakes bite both as a method of hunting and a means of protection. The WHO once again lists snakebite as a neglected disease.

Out of an average of 5 million snakebites annually, worldwide with around 2.5 million envenomations and 30,000–125,000 deaths, Indian Subcontinent constitutes more than 50% of the share, partly because of the ignorance, prevalence of old practices (Ojha & mantras), and the lack of proper medical facility in far flung areas. There are about 216 species of snakes in India out of which
52 are venomous. Broadly speaking there are four major families of venomous snakes:

- Viperidae, with sub class
  - viperinae the old world vipers and
  - crotaline new world and Asian pit vipers
- Elapidae the cobras, kraits, coral snakes, sea snakes, and all venomous Australian snakes
- Lamprophiidae (subfamily Atractaspididae the burrowing asps)
- Colubridae (a large family in which most of species are non-venomous with only a few being dangerously toxic to mankind)⁴

The vipers are mostly hemotoxic and cardiotoxic but occasionally may also be neurotoxic. The Elapidae are mostly neurotoxic but may affect the cardiac as well as the vascular system causing sudden deaths or coagulopathy. Most snake venoms contain multiple toxins ranging from cytotoxins, hemotoxins, neurotoxins, bungarotoxins, cardiotoxins, and myotoxins, which comprise of different types of peptides and proteolytic enzymes, glycoproteins, metal ions and hyaluronidases, phospholipases, etc. The most commonly found examples of viperidae are Russel viper, pit viper, the commonly found elapids are Cobra (Naja naja) and common krait (Bungarus caeruleus).

Poisoning by most viperids and some elapids with necrotizing venoms causes progressive local swelling, pain, ecchymosis, and hemorrhagic bullae or serum filled vesicles. In serious bites tissue loss can be significant. Systemic finding may include change in taste, mouth numbness, persistent severe vomiting and/or abdominal pain, muscle fasciculations, arrhythmias, for example, tachycardia or bradycardia, torsades-de-pointes, ventricular fibrillation, hypotension, shock, pulmonary edema, hemorrhage from any site and renal dysfunction. Poisoning by neurotoxic elapids such as kraits, many Australian elapids (Atractaspis spp.) and tiger snakes (Notechis spp.), cobras and some viperids cause neurologic dysfunction, starting with cranial nerve involvement like ptosis, external ophthalmoplegia, altered mental status progressing to bulbar paralysis, and/or general paralysis involving the muscles of respiration leading to death. Most
often the patient has been brought to us in an unconscious state without any history of snakebite in the absence of any fang marks but a history of having slept on the floor. After elapid bites, the time of onset of envenomation varies from minutes to hours depending upon the species involved, the anatomic location of the bite, and the amount of venom injected.

**Management**

*Basic management at the location of bite:* It involves retardation of absorption of venom and neutralization of venom as quickly as possible. The most important management of snakebite of any type remains as ever reassurance, the mere fact of a snakebite frightens the boldest of the persons at times to fainting attacks, so assuring a person that nothing lethal has happened will not only prevent him from collapsing but will also prevent the adrenaline secretion resulting in increased heart rate, and enhanced dissipation of the venom in circulation and its immediate effects. The person should be made comfortable by lying down and placing the part bitten below the level of heart and stabilizing it with a splint so as to cause minimum movement, and hence prevent absorption of the poison. Even if there are no visible fang marks and the snake is apparently non-poisonous the basic management should remain the same, because most of neurotoxic snakebites (common krait) cause minimum pain and little or no visible fang marks. No tourniquets (tight ligatures) to be applied in any case which will result in complication than help, rather remove any rings, watches, bracelets or anything around the bitten part, which may act as a tourniquet once the part swells-up. The person should be made to be fully aware given plenty of fluids and talked to incessantly. If there are minimal fang marks and no ecchymosis or swelling a soft elastic bandage should be applied proximal to the bite through which the little finger can be easily passed (neurotoxic bite, vide-supra). Incising of the wound, applying electric current or suction should be avoided because they can enhance local tissue damage. Similarly, the application of poultices and ice packs should be strongly discouraged. In case of hemorrhagic symptoms the best plan is to stabilize the part with a splint and keep it below the level of heart and wash it with soap and water no pressure or incision to be given in any case. Watch for bleeding from any site and as mentioned above if there are chances of hemorrhagic shock then fluids orally need to be increased and the patient carried on a cot or stretcher to the nearest hospital/dispensary which has the polyvalent anti-venin serum (AVS) available.

*Hospital management:* The patient should be closely monitored at least for 24 hours even if there are no fang marks and the snake was apparently non-poisonous (vide-supra). A care should be taken of airway, blood pressure, respiration, heart rate, and neurological status/deficit, while taking the history and performing a preliminary clinical examination. In case of viper bites the level of swelling of the bitten extremity should be noticed and diameter measured half hourly and the part placed below the heart level till AVS is instituted. The bands or tourniquet if applied should be very slowly removed after a large bore Intravenous access so as to prevent the sudden release of acidic blood collected in the distal part to the central circulation which may result in bradycardia or hypotension leading to shock and sudden death. A sample of 3–5 mL of venous blood should be immediately drawn and poured in to a dry test tube which should be placed vertically so as to see for 20 minute whole blood clotting time (20 WBCT) and tilted to 45° at 4–6 hours intervals so as to assess for coagulopathy and further institution of AVS. In addition other blood chemistry and measurements like thrombocyte count, renal and hepatic functions, coagulation studies, and urine for fibrin degradation products to diagnose consumptive coagulopathy and for blood and myoglobin should be carried out. If the bitten part is swollen due to intra-compartmental bleed the part should be raised above the heart level after starting AVS and if it does not respond to conservative measurements then Mannitol (1 gm/kg fast) should be infused to release the pressure. Arterial blood gas (ABG) studies, electrocardiography, and chest radiography may be carried out in severe envenomation when there is no active bleeding going on. In case of neurotoxic poisoning a care should be taken about ptosis, drooling of saliva, respiratory insufficiency, or other types of neurodeficiency.

The hub of treatment of venomous snakebite, resulting in significant envenomation is the administration of specific AVS. These sera are obtained from the sera of animals after, either by the injection of the venom of common varieties of snakes obtained by milching them (Fig. 4) or by giving them a direct bite. The AVS
available in our country is a polyvalent one, which acts as an antidote to the most of the types of snake venoms involved in our country. Produced either at Haffkine’s Institute, Mumbai, or National Serum Institute Kassauni (Himachal Pradesh). The goal of AVS administration is to allow antibodies (or antibody fragments) to bind up circulating venom components before they can attach to target tissues and cause deleterious effects. Because the hemotoxic snake venom due to its procoagulants and anti-coagulants causes venum induced consumptive coagulopathy through its toxins exerting effect on the platelets, coagulation factors, coagulation products and blood vessels, the administration of AVS should be strictly according to the nature of the clot, that is, if no clot forms within 20 minutes full dose of AVS to be instituted (100 units stat) and firmer the clot lesser the dose of AVS. Some studies have also mentioned the role of liver gene regulation in hemostasis.

Since the heterologous sera, obtained from any source, being a foreign body carry their own risks like acute, non-allergic/allergic anaphylaxis and delayed type hypersensitivity reactions (serum sickness) skin testing for potential allergy is a must although our practice has been to administer 100 mg of hydrocortisone IV before starting AVS even if the intradermal test was ambiguous or in the alternative 0.01 mg/kg, up to 0.3 mg of epinephrine subcutaneous or intramuscularly. The indications for administration of AVS to victims of bites by vipers or elapids depend upon:

- Presence of systemic symptoms or signs (vide-supra), persistent and severe vomiting and/or abdominal pain and/or laboratory abnormalities and significant progressive local findings (massive local necrosis, soft tissue swelling crossing a joint or involving more than half the bitten limb or continuous bleeding from any site, internal or external). In case of neurotoxic poisoning the administration of AVS is indicated at the first sign of any neurotoxicity (ptosis, difficulty in swallowing or signs of peripheral neuropathy).
- Modest expansion of patients’ intravascular volume with crystalloids also may blunt acute adverse reactions, hence their administration should be concomitant with IV administration of AVS, which should be started in the presence of a doctor and closely monitored by him for any adverse reactions like acute bronchospasm or cardiovascular collapse.

**Specific Treatment**

- **Hemotoxic/Cardiotoxic bite:** The patient presenting with a local swelling or bleed or ecchymosis or signs of bleeding from any part (mouth, gums, hematemesis/melaena) signs of cardiovascular failure and apprehension.
  - Reassurance.
  - Administration of tetanus toxoid.
  - Establish two large bore IV lines with normal saline/crystalloid starting with a bolus 20–40 mL/kg body weight if the patient is hypotensive, if in shock treat it.
  - Maintenance of proper airway, breathing, blood pressure, and raise the swollen part above the level of heart once AVS is started.
  - Urgent clotting time estimation (CT) vide-supra 4–6 hours (Reid criteria).
  - Intradermal test of AVS and thereafter 100 mL (ten vials of lyophilized/liquid polyvalent AVS) in 500 mL of normal saline over a period of 4–6 hours to be preceded by 100 mg of hydrocortisone (in case of doubtful test).
  - The above dose to be repeated after 6 hours if the blood remains non-clotting (>20 minutes depending upon the quality of clot) (Reid criteria).
  - If the swelling in the bitten extremity points toward subfascial muscle edema impeding tissue perfusion (muscle compartment syndrome) IV

![Fig. 4: Russell’s viper snake](image-url)
mannitol (1 gm/kg) may be administered in a hemodynamically stable patient. However, if the response is not proper, fasciotomy of the limb may be needed after orthopedic consultation. AVS must be administered in all cases presenting in an acute form with active bleeding even if presenting after 3–4 weeks of bite.

- Antibiotics effective against staph like cloxacillin/cephalexin 500 mg 8 hourly. In case of massive necrosis and skin and muscle damage metrogyl should be added.
- The amount of AVS administered depends upon the clinical response and is inversely proportional to the quality of the clot (i.e., poor clot, more AVS and good clot less AVS. Watch the clot for 4 hours because at times the clot may redissolve). No fixed dose of AVS has been calculated so far.

- **Neurotoxic bites:**
  - Reassurance
  - Maintenance of proper airway, breathing, blood pressure, and watch for signs of neurodeficiency like altered mental status, ptosis, drooling of saliva, difficulty in swallowing, diplopia, difficulty in breathing or signs of peripheral neuropathy, paralysis, or unconsciousness.
  - Intradermal test of AVS and thereafter 100 mL (ten vials of lyophilized/liquid polyvalent AVS) in 500 mL of normal saline over a period of 4–6 hours to be preceded by 100 mg of hydrocortisone (in case of doubtful test).
  - Atropine 0.6 mg IV (children, 0.02 mg/kg; minimum of 0.1 mg) follow with:
    Edrophonium: 10 mg IV (children, 0.25 mg/kg)
    Or
    Neostigmine 1.5–2 mg IM (children, 0.025–0.08 mg/kg)

    Continue neostigmine at a dose of 0.5 mg (children, 0.01 mg/kg) IV or S/C every 30 minutes as needed, with continued administration of atropine by continued infusion of 0.6 mg over 8 hours (children 0.02 mg/kg over 8 hours). Stop this regimen if no relief is evident after three doses because in that case the bite is that of a krait.

    Maintain vigilance regarding aspiration risk and secure the airway with endotracheal intubation as needed and put on ventilator if still not responding.
    - Continue to repeat the AVS dose till substantial relief or death of the patient.

- In case of an acute reaction to AVS the infusion should be temporarily stopped and the reaction immediately treated with intramuscular epinephrine 0.01 mg/kg up to 0.03 mg, antihistamines (diphenhydramine, 1 mg/kg to a maximum of 100 mg and cimetidine, 5–10 mg/kg to a maximum of 300 mg and glucocorticoids (200 mg IV). Once the reaction is controlled if the severity of poisoning warrants additional AVS, the dose should be diluted further in isotonic saline and restarted as soon as possible. Rarely in recalcitrant cases desensitization needs to be done with hydrocortisone (starting from 400 mg hourly and tapering till normalization or a concomitant IV infusion of epinephrine may be required to hold allergic sequelae at bay while further AVS is administered). The patient must be monitored very closely, preferably in an intensive care setting, during such therapy.

- Blood and blood products are rarely necessary in the management of a hemotoxic bite, although these bites can cause a drop in platelet count or hematocrit and depletion of coagulation factors these usually rebound within hours after administration of adequate amount of AVS. Even if there is a great need for these products they should be given only after adequate AVS administration to avoid adding fuel to the fire of ongoing coagulopathy.

- Patients who develop acute renal failure due to rhabdomyolysis or hemolysis should be managed in a conventional fashion, as the insult is one of acute tubular necrosis and is frequently reversible and if not responding should be referred to a nephrologists for hemodialysis or peritoneal dialysis.

- A dry, sterile dressing should be applied to the wound while splinting with padding between the digits. Pain control should be achieved with paracetamol or codeine. Salicylates and other non-steroidal anti-inflammatory agents should not be used because of their effect in prolonging clotting of blood.

- After full care of the wound and normal clotting of blood, physiotherapy should be instituted for return to a functional state. The victim should keep contact with the treating physician even after discharge and be made aware about signs and symptom of wound infection, AVS related serum sickness and long-term sequelae like pituitary insufficiency, with central diabetes insipidus in Russel viper bites and the late onset of coagulopathy after 2–3 weeks of bite and to
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avoid elective surgery or activities involving high risk of trauma. The serum sickness should be treated with prednisone (1–2 mg/kg daily) until all findings resolve and then tapered over 1–2 weeks, besides oral antihistamines and analgesics.

Morbidity and Mortality
The mortality in India is high because of religious beliefs (witchcrafts and mantras) lack of connectivity and ignorance in both, the treater and the treated (vide-supra). Similarly, the incidence of morbidity (permanent functional loss in a bitten extremity) is also substantial due to muscle, nerve, or vascular injury or to a scar contracture with resulting inability to work and earn a proper living.

Future Aspects
In the biggest democracy of the world which boasts of free medical care for all and when we are planning to land at Mars, a substantial portion of the population either loses life or is mauled permanently due to a preventable cause. The following main points which need to be addressed are:

- Education of the masses about the prevalence of the types of snakes and their proliferation at a particular time of the year (summer and monsoon) and at specific places (farmland, mudhouses, ruins, forests) and use of proper gear (covering the lower limbs up to knees and the upper limbs up to elbows with long boots and thick gloves or in the alternative with thick wrappings like jute, etc. and use of a lathi and torch/lamp when going to fields/forests or working at extremes of times makes it easily preventable). Digging of a shallow ditch around the Jhuggis as the defense personnel do around their tents. Special care needs to be taken during floods, which not only bring the snakes out of their burrows but also from far off places.
- Availability of proper amount of AVS (which is available) and qualified persons at subcenters of the health department which already exist to orientate them and to make them more conscious about envenomation and its management because the ultimate treatment of any type of snakebite poisoning is only timely administration of AVS besides other remedial measures.
- Since this is mainly a problem of developing countries only, a combined research should be oriented toward production of a snake venom vaccine/venom toxoid for those people who are prone to snakebite poisoning like the farmers, the foresters, the trackers, and the migrant laborers who sleep on the ground.
- Some trials are being given to the use of PLA2 inhibitor Varespladib as an alternative to AVS because of its effective inhibition of snake phospholipase. Some local people have also used Citrus peels locally but again it is firmly stressed to follow only the above standard guidelines because human life is invaluable and does not need to be experimented with.

Conclusion
Snakes, an essence of the Universe, have been created by the almighty, like human beings to take care of the rodents and other insects, which otherwise would cause immense loss to the mankind. Worshipped in some civilizations and hated in others, the Snakes find an important place in our Medical emblems. In the West they are being nurtured as pets as well since the Roman Empire. Still a word of caution is essential when dealing with them, especially in certain seasons like rains and floods which cause a surge in their population and activity. For the defense personnel, forest employees, trackers, and explorers like archaeologists a proper gear needs to be worn and a lathi and torch for the house holder are a must and only antidote of snake bite poisoning the AVS though available liberally needs to be used judiciously. Similarly, a lot of old remedies like laceration, tourniquet, and application of electric current need to be discarded. Neurotoxic snake bite should be ruled out in all unconscious patients in the planes, especially during rainy sessions. New drugs are in the pipeline but till their confirmed benefit AVS should be the hallmark of treatment.

Since a neglected problem, especially of the developing countries a combined effort to develop an anti-toxin or vaccine of universal usage is the need of the hour and may be the answer as has been very fortunately carried out in the case of COVID-19 in less than a year.

References