When to use Antivenom

Dr. T. S. Srinath Kumar

President – Society for Emergency Medicine, India,

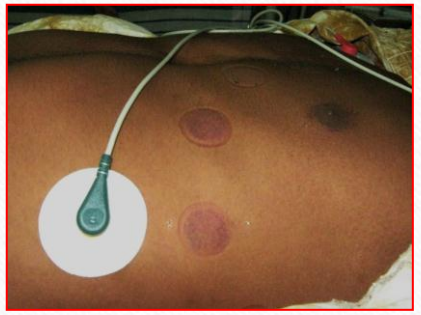
Asst. Treasurer – Asian Society for Emergency Medicine

Advisor – Special Board for Emergency Medicine, National Board of Examinations

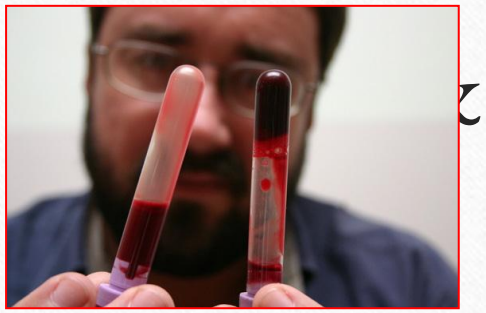
Editor – Eurasian Journal of Emergency Medicine

Head & Group Coordinator – Narayana Hrudayalaya, Bangalore

A 20 yr male



Pallor +
Icterus –
Cyanosis –
Clubbing –
Lymphadenopthy + tender nodes rt inguinal
Edema @ bite site Rt foot
Vitals – HR – 90/mt, BP – 120 /90mmhg, SpO2 – 98% Room air



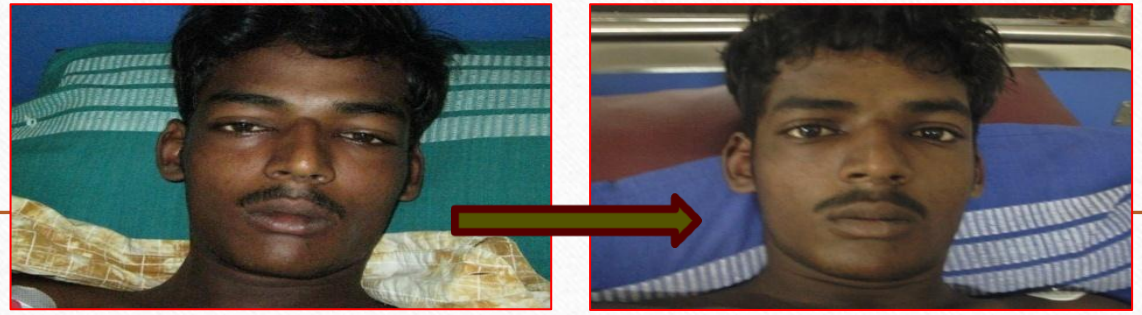
Total no. of HD till 26/6/10

Date	18/6	19/6	20/6	21/6	22/6	23/6	24/6	25/6
Ur	163	110	92	90	55	98	66	110
Cr	2.7	3.1	5.8	4.8	3.8	3.1	6.0	8.1
HD								
Duration in hrs	3	4	4	4		4		4
Ltrs removed	1.5	1.5	1.5	4.6		2.5		2.5

Investigations & Blood Products

	18/6	19/6	20/6	21/6	22/6	23/6	24/6	25/6
HB	19.2		9.6	10.6	10.4	10.0	10.3	
PLT	14,000		28,000	42,000	85,000	1,99,000	2,75,000	
BT			14:30		3:30	4:30	3:25	
CT	15:00				11:00	11:00	4:10	
PT								
Pt val	38.6		13.4					
INR	3.06		1.06					
APTT								
Pt val	33.1		22.0					
FFP	6	6						
Plt con	4	4	4	4				

72 vials later…..



Platelets- 14,000 → 1,99,000

ASV stopped on 23/6/10

Anti Snake Venom

- Pepsin-refined immunoglobulins that has been separated from the serum of horses.
- These horses are usually hyper-immunised with snake venom.

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- In an anti venom institute various species of snakes are bred.
- When mature enough they are introduced into a milking room.
- Professionals grab the snakes with thumb and index finger at the back of the head behind the angle of the jaw.
- This allows for them to press the snakes glands with a minimal risk for being bitten by the snake.
- A minimal quantity of venom will be extracted each time, so snakes have to be milked many many times for a useful amount of venom to be produced.

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- Horses are usually used to create anti venom. (Goats, sheep, chickens, camels, donkeys rabbits cats and rodents may also be used. Sharks have also been used. But introduces obvious difficulties)

- After careful measure and dilution it is injected into the horse under close supervision.

- Antibodies in the horse serum usually peak in eight to ten weeks.

- Blood is harvested from the jugular vein. 3 – 6 liters of blood is drained.

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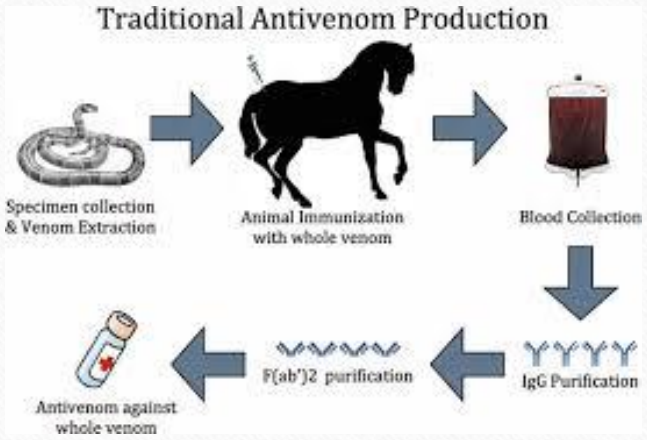
- Blood is centrifuged to separate out the plasma.
- The anti venom is then separated out of the plasma.
- Different institutes have their own methods. Usually the unwanted proteins are precipitated out by adjusting the pH or adding salts to the solution. (Exactly how for most institutes is a closely guarded secret)
- Final step includes breaking down the antibodies enzymatically and separating out the active ingredient.



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When to Give?

Big Five Snakes

Snake Bite

- On Site Primary Survey (First Aid)
- Rapid Transport
- Treatment In Hospital
- Rehabilitation

R.	Reassure the patient. 70% of all snakebites are from non-venomous species. Only 50% of bites by venomous species actually envenomate the patient.
I.	Immobilise in the same way as a fractured limb. Use bandages or cloth to hold the splints, not to block the blood supply or apply pressure. Do not apply any compression in the form of tight ligatures, they don't work and can be dangerous!
GH.	Get to Hospital Immediately. Traditional remedies have NO PROVEN benefit in treating snakebite.
T.	Tell the doctor of any systemic symptoms such as ptosis that manifest on the way to hospital.

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TRADITIONAL METHODS THAT NEED BE DISCARDED

Tourniquets
Cutting and Suction
Washing of wounds
Electrical Therapy and Cryotherapy

Newer Methods Considered Inapplicable in the Indian Context

Pressure Immobilization Dressing.

Handling Tourniquets

- Before removal, test for the presence of a pulse distal to the tourniquet.
- Be prepared to handle complications such as sudden respiratory distress or hypotension.
- Blood pressure cuff can be applied to reduce the pressure slowly.

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Patient Assessment Phase On arrival.

- Airway, Breathing and Circulation.
- Give Tetanus Toxoid where there is evidence of bite.
- Routine use of anti-biotic is not necessary, to be considered if there is cellulitis or necrosis.

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Pain

- Paracetamol. Adult dose of 500-1000mg & Pediatric dose 10mg/kg 4-6 hourly orally.
- Aspirin and NSAIDs avoided due to its adverse impact on coagulation.
- Opiates such as Tramadol, 50 mg used orally for relief of severe pain. In a tertiary centre, tramadol may be given IV.

Diagnosis Phase: General Principles

- If possible identify the snake. Snake colouration is unreliable, as is most of the advice given concerning pupil shape and scalation. Have the victim carefully bring the snake to hospital if it has been killed.
- **All patients will be kept under observation for a minimum of 24 hours.**. In India bite marks are of no use in identifying if a species is venomous or not.. Many venomous species have more than two fangs.
- Determine if any traditional medicines have been used, they can sometimes cause confusing symptoms.
- Determine the exact time of the bite. This can give indications as to the progression of any symptoms.
- What was the victim doing at the time of the bite. Some activities such as grass cutting or feeding stock animals in the evening mzy be suggestive of snakebite.

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Diagnosis Phase: Symptoms

Feature	Cobras	Kraits	Russells Viper	Saw Scaled Viper	Hump Nosed Viper
Local Pain/ Tissue Damage	YES	NO	YES	YES	YES
Ptosis/ Neurological Signs	YES	YES	YES!	NO	NO
Haemostatic abnormalities	NO	NO!	YES	YES	YES
Renal Complications	NO	NO	YES	NO	YES
Response to Neostigmine	YES	NO?	NO?	NO	NO
Response to ASV	YES	YES	YES	YES	NO

Syndromes as per WHO

- Syndrome 1 –

  local Envenomation with bleeding / clotting disturbances

Syndrome 2 –

1 + shock or Acute kidney injury, neurological signs like ptosis, external opthalmoplegia , facial paralysis and dark brown urine

Syndrome 3 –

2 + Paralysis

Syndrome 4 –

Paralysis without signs of local envenomation signs

bitten on land while sleeping

bitten in the sea or fresh water lakes

Syndrome 5 –

Paralysis, bleeding disorders, Acute kidney injury

Diagnosis Phase: Investigations

20 Minute Whole Blood Clotting Test (20WBCT)

- Considered the most reliable test.
- A few mL of fresh venous blood is placed in a new, clean and dry glass vessel (preferably a small glass testube and left at ambient temperature for 20 minutes. The glass vessel should be left undisturbed for 20 minutes and then gently tilted, **not shaken**. If the blood is still liquid then the patient has incoagulable blood.
- The vessel must not have been washed with detergent as this will inhibit the contact element of the clotting mechanism.
- Carried out every 30 minutes from admission for three hours and then hourly after that. If incoagulable blood is discovered, the 6 hourly cycle will then be adopted to test for the requirement for repeat doses of ASV.

Other Useful investigation

- Haemoglobin/ PCV/ Platelet Count/ PT/ APTT/ FDP/ D-Dimer Peripheral Smear.
- Urine Tests for Proteinuria/ RBC/ Haemoglobinuria/ Myoglobinuria.
- Biochemistry for Serum Creatinine/ Urea/ Potassium.
- Oxygen saturation/ PR/BP/ RR/ Postural Blood Pressure.

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ONLY if a Patient develops one or more of the following signs/symptoms will ASV be administered:

Systemic envenoming

- Evidence of coagulopathy: Primarily detected by 20WBCT or visible spontaneous systemic bleeding, gums etc.
- Further laboratory tests for thrombocytopenia, Hb abnormalities, PCV, peripheral asmear etc provide confirmation, but 20WBCT is paramount.
- Evidence of neurotoxicity: ptosis, external ophthalmoplegia, muscle paralysis, inability to lift the head.

- Saini V, Sardana D, Samra T. Management of snake bite victims in a Tertiary Care Intensive Care Unit in North India. *Indian J Crit Care Med*. 2014;18(8):544–545. doi:10.4103/0972-5229.
- Guidelines I. Snake Bite: Indian Guidelines and Protocol.
- Mohapatra BN, Mohanty CBK. Guidelines for Anti Snake Venom Therapy.

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Severe Current Local envenoming

- Severe current, local swelling involving more than half of the bitten limb (in the absence of a tourniquet).
- In the case of severe swelling after bites on the digits (toes and especially fingers) after a bite from a known necrotic species.
- Rapid extension of swelling (for example beyond the wrist or ankle within a few hours of bites on the hands or feet).
- **Swelling a number of hours old is not grounds for giving ASV.**

- Saini V, Sardana D, Samra T. Management of snake bite victims in a Tertiary Care Intensive Care Unit in North India. *Indian J Crit Care Med*. 2014;18(8):544–545. doi:10.4103/0972-5229.138164.
- Guidelines I. Snake Bite: Indian Guidelines and Protocol.
- Mohapatra BN, Mohanty CBK. Guidelines for Anti Snake Venom Therapy.

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In the Indian context one of these two categories will be the sole determinant of whether ASV is administered to a patient.

- Cardiovascular abnormalities: hypotension, shock, cardiac arrhythmia, abnormal ECG.
- Persistent and severe vomiting or abdominal pain.

- Saini V, Sardana D, Samra T. Management of snake bite victims in a Tertiary Care Intensive Care Unit in North India. *Indian J Crit Care Med*. 2014;18(8):544–545. doi:10.4103/0972-5229.138164.
- Guidelines I. Snake Bite: Indian Guidelines and Protocol.
- Mohapatra BN, Mohanty CBK. Guidelines for Anti Snake Venom Therapy.

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- A Study was done at one of our institutes to assess the reliability of 20 minute whole blood clotting test (20WBCT) as an indicator of low plasma fibrinogen level concentration in snake bite victims.

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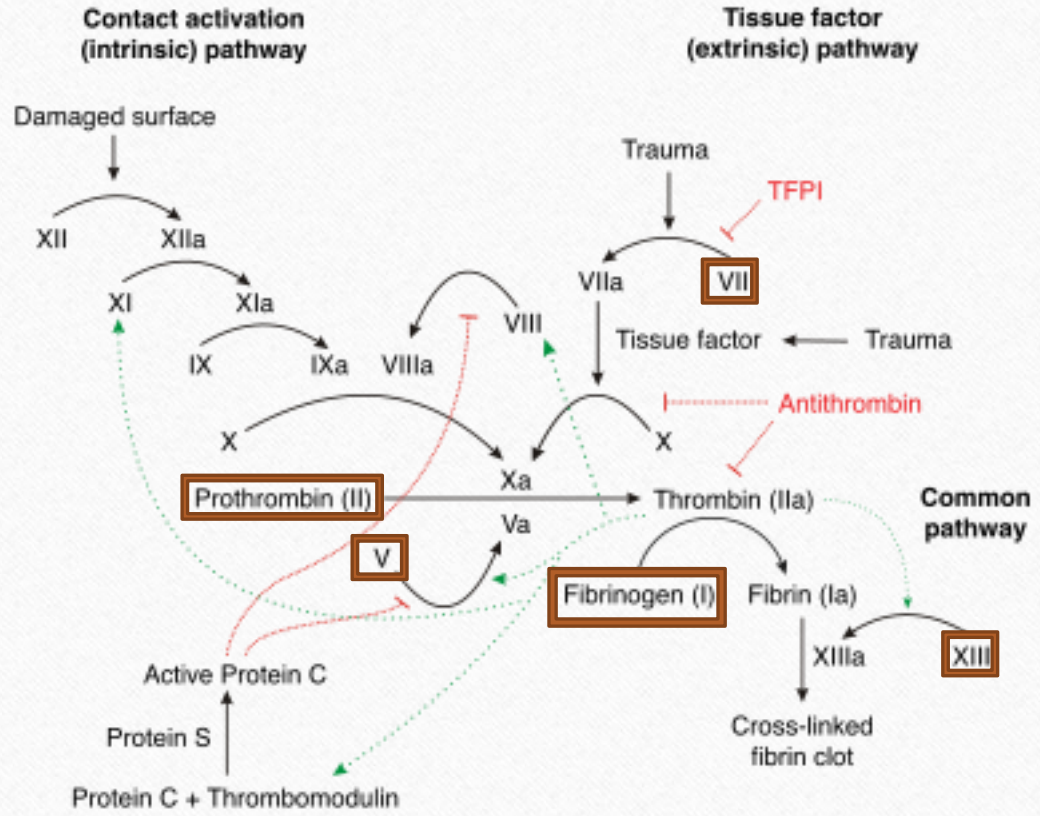
- Hematological complications of the venom is mainly due to depletion of fibrinogen Factors V, VII, II and XIII.



- Bashir R, Jinkins J. Cerebral infarction in a young female following snake bite. *Stroke*. 1985;16(2):328–330. doi:10.1161/01.STR.16.2.328

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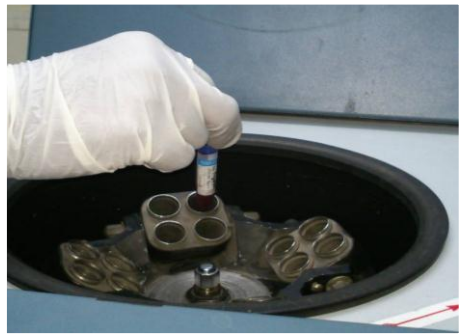
A B C D

Fig 5: A- Clean dry test tube, B- 2ml blood collected and left undisturbed for 20mins, C- Tube tilted after 20mins and if blood not clotted, then 20WBCT Positive, D- If blood not clotted then 20WBCT Negative

Both 20WBCT and Plasma Fibrinogen levels are repeated twice a day, till both the tests are normal in three consecutive readings. The patients are treated according to the Snake Bite Protocol followed in the hospital. The comparison between 20WBCT and Plasma Fibrinogen levels were analysed statistically.

A



B

C

D

E

Fig 6: Plasma Fibrinogen Test, A- Trisodium citrate containing test tube, B- 5ml blood collected and centrifuged for 15mins, C- Plasma separated, D- The sodium azide (buffer solution) diluted plasma is taken is kept in the automated machine (Coagulation analyser), E- Lyophilised titrated calcium thrombin is added at 60secs of the commencement of the test

22 treated at outside with blood products

5 with h/o intake of anticoagulants

Excluded 27

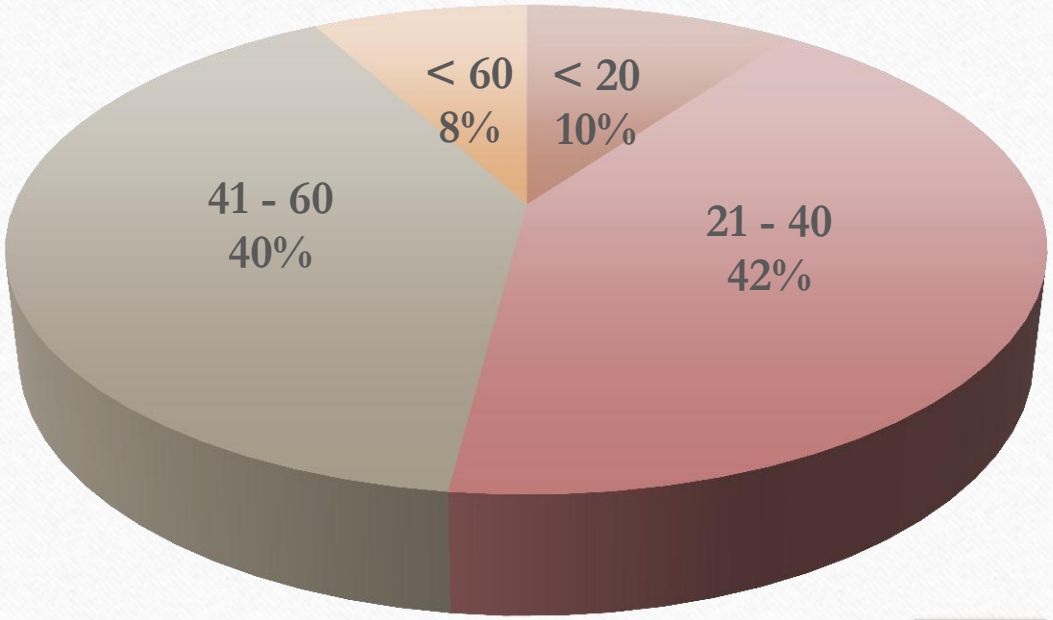
100

Included 73

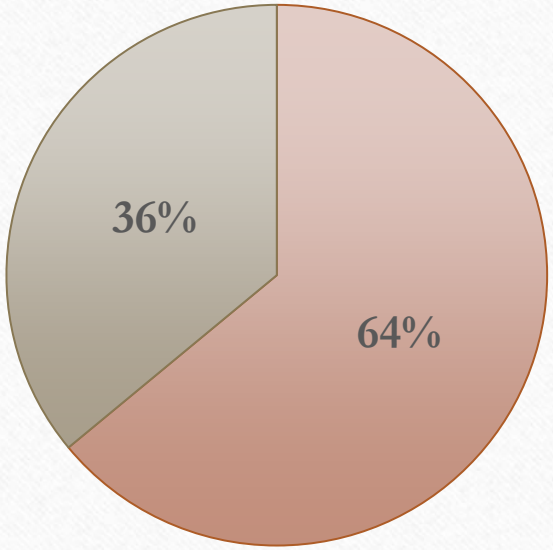
43 with history of snake bite

30 with history of unknown bite

Age wise Distribution



Gender Wise Distribution



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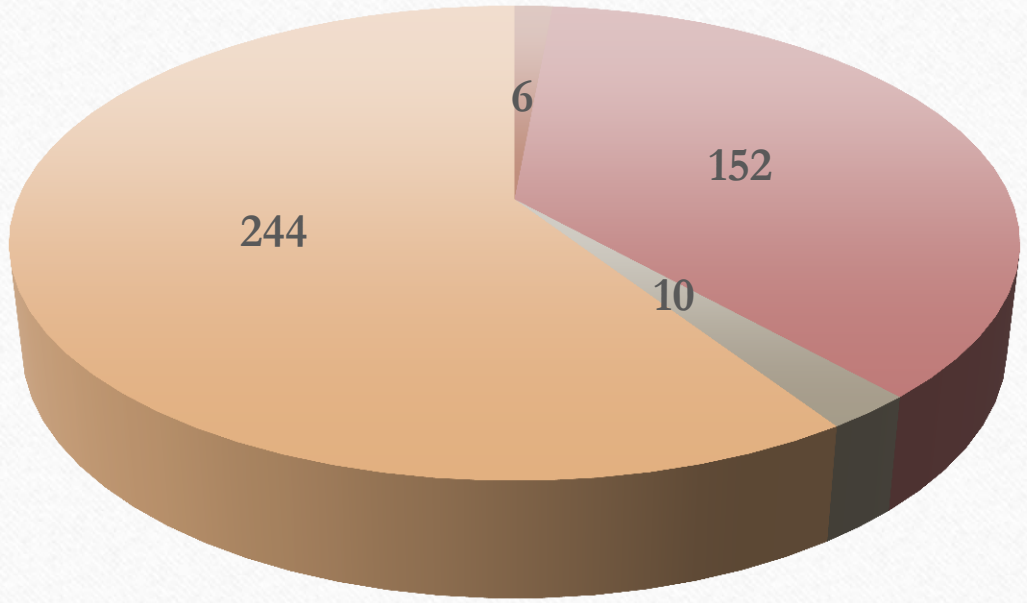
	Low Fibrinogen Levels	Normal Fibrinogen Levels	Total
Positive 20WBCT	152 (a)	6 (b)	158 (a + b)
Negative 20WBCT	10 (c)	244 (d)	254 (c + d)
Total	162 (a + c)	250 (b + d)	412 (a + b + c + d)

a = True Positive
b = False Positive
c = False Negative
d = True Negative



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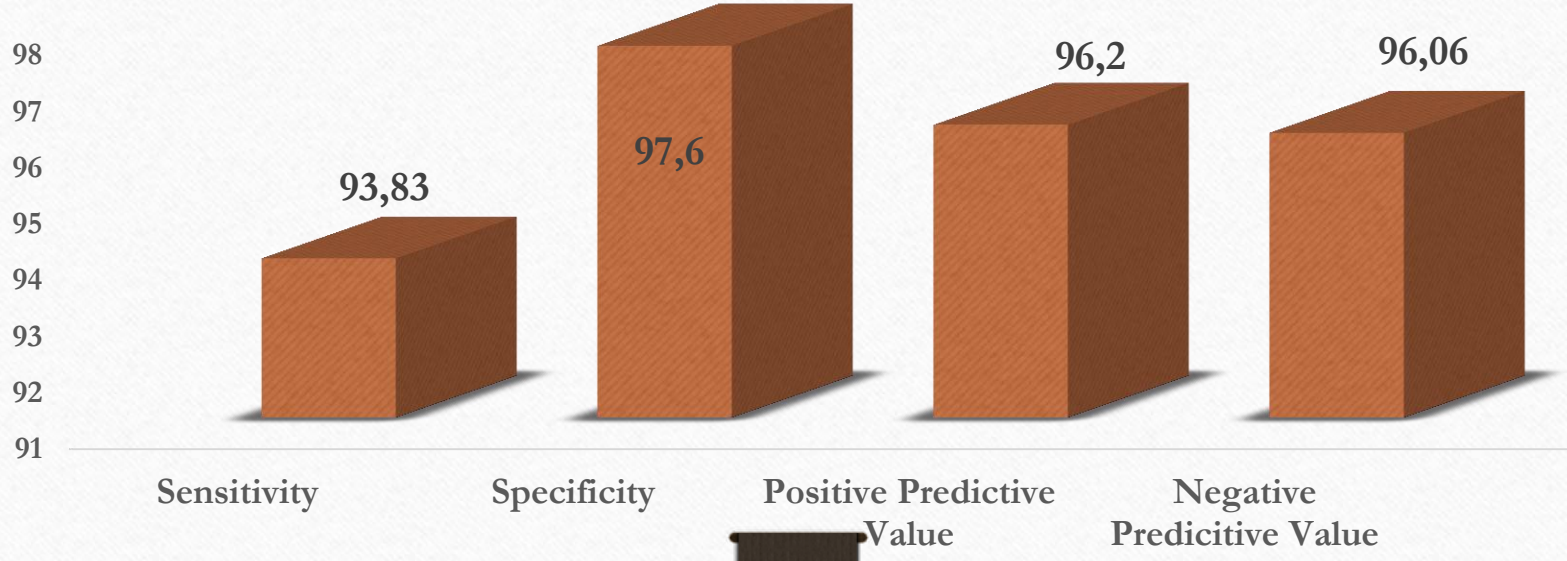
Sensitivity	$\frac{a}{a+c}$	0.93 (93.83%)
Specificity	$\frac{d}{b+d}$	0.97 (97.6%)
Positive predictive values	$\frac{a}{a+b}$	0.96 (96.2%)
Negative predictive values	$\frac{c}{c+d}$	0.96 (96.06%)



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How to Give?

ASV

- Each ml neutralize
  - 0.6 mg of cobra
  - 0.6 mg of rusells viper
  - 0.45 mg of krait
  - 0.45 mg of saw-scaled
- Average yield / bite
  - Cobra- 60 mg
  - Rusells- 63 mg
  - Krait- 20 mg
  - Saw-scaled- 13 mg

Prevention of ASV Reactions – Prophylactic Regimes

NO ASV TEST DOSE MUST BE ADMINISTERED

- 100mg of hydrocortisone and H1 antihistamine (10mg chlorphenimarine maleate; 22.5mg IV phenimarine maleate IV or 25mg promethazine HC1 IM) 5 minutes before ASV administration.
- The dose for children is 0.1-0.3mg/kg of antihistamine IV and 2mg/kg of hydrocortisone IV. Antihistamine should be used with caution in paediatric patients.
- 0.25-0.3mg adrenaline 1:1000 given subcutaneously.

- Saini V, Sardana D, Samra T. Management of snake bite victims in a Tertiary Care Intensive Care Unit in North India. *Indian J Crit Care Med*. 2014;18(8):544–545. doi:10.4103/0972-5229.138164.
- Guidelines I. Snake Bite: Indian Guidelines and Protocol.
- Mohapatra BN, Mohanty CBK. Guidelines for Anti Snake Venom Therapy.

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ASV is recommended to be administered in the following initial dose:

Neurotoxic / Anti Haemostatic 8-10 Vials

Children receive the same ASV dosage as adults. The ASV is targeted at neutralising the venom. Snakes inject the same amount of venom into adults and children.

ASV can be administered in two ways:

- Intravenous Injection: reconstituted or liquid ASV is administered by slow intravenous injection. (2ml/ minute). Each vial is 10ml of reconstituted ASV.
- Infusion: liquid or reconstituted ASV is diluted in 5-10ml/kg body weight of isotonic saline or glucose.

All ASV to be administered over 1 hour at constant speed.

The patient should be closely monitored for 2 hours.

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Repeat Doses: Anti Haemostatic

The ASV strategy will be based around a six hour time period. When the initial blood test reveals a coagulation abnormality, the initial ASV amount will be given over 1 hour.

No additional ASV will be given until the next Clotting Test is carried out.

After 6 hours a further coagulation test should be performed and a further dose should be administered in the event of continued coagulation disturbance. This dose should also be given over 1 hour. CT tests and repeat doses of ASV should continue on a 6 hourly pattern until coagulation is restored, unless a species is identified as one against which Polyvalent ASV is not effective.

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Repeat Doses: Neurotoxic

If the symptoms have worsened or if the patient has gone into respiratory failure then a further dose should be administered, after 1-2 hours. At this point the patient should be re-assessed. If the symptoms have worsened or have not improved, a second dose of ASV should be given.

This dose should be the same as the initial dose, i.e. if 10 vials were given initially then 10 vials should be repeated for a second dose and then ASV is discontinued. 20 vials is the maximum dose of ASV that should be given to a neurotoxically envenomed patient.

Once the patient is in respiratory failure, has received 20 vials of ASV and is supported on a ventilator, ASV therapy should be stopped. (As per Health and Family Welfare

- “ *the disappearance of venom antigenemia* following antivenom administration is a surrogate endpoint to measure accurately the efficacy of antivenom “

  - Journal of medical toxicology vol 5, no. 4, dec 2009

Journal of the association of physicians of india • june 2013 • VOL. 61

Table 3 : Outcome according to bite to needle time

Variables	**Bite to needle time**				**P value**
	0-2 hrs	**2- 4 hrs**	**4-6 hrs**	**>6 hrs**	**All patients**
Recovered	20(38.5%)	18(34.6%)	9(17.3%)	5(9.6%)	52(100.0%) 0.015*
Died	0	0	0	2(100.0%)	2(100.0%) 0.015*
Total	20(37.1%)	18(33.3%)	9(16.7%)	7(12.9%)	54(100.0%) -

Raina S, Raina S, Kaul R, Chander V, Jaryal A. Snakebite profile from a medical college in rural setting in the hills of Himachal Pradesh, India.

Indian J Crit Care Med 2014;18:134-8Twenty-fi ve cases of snake bite were admitted in our Intensive Care Unit (ICU) from October 2012 to September 2013; three-fourth of them presented from June 2013 to September 2013. Patients with fang marks and swelling, cellulitis, bleeding, and blisters formation at the local site were included; any patient with suspicion of snake bite but no direct evidence was excluded. Mean age was 31.16 years (range: 13-70 years) and male to female ratio was 18:4.All patients presented with neuroparalytic features and reported of snake bite in the night during sleep. The mean duration of the ICU stay was 4.32 days (range: 3-13 days). The mean dose of equine polyvalent antisnake venom (ASV) administered was 48.63 vials (range: 40–60 vials). No patient had any adverse reactions to the antivenom. No other complication, namely acute renal failure, acute respiratory distress syndrome, cortical venous thrombosis or disseminated intravascular coagulation was reported during hospitalization. They were mechanically ventilated for a mean period of 3.18 days.

Case Report # 1

- 40 yr old male bitten by snake 6 weeks back presented with quadriparesis. Electrophysiological studies confirmed GBS
- He was subjected to plasmapheresis & discharged. Follow-up after 6 mths- resumed working
    - Srivastava A, Taly AB, Gupta A, Moin A, Murali T. Guillain-Barre syndrome following snake bite: An unusual complication. Ann Indian Acad Neurol 2010;13:67-8

Case Report # 2

- 27 day old **neonate**, presented wih neurotoxic envenomation
- Given totally 50 vials ASV
- The reversal of respiratory and neuromuscular paralysis was used as the end point of antivenom therapy
- No neurological or developmental delay was observed after a follow up of 12 weeks
    - Jindal et al; ASV in a neonate with snake bite; Indian paediatrics : VOLUME 47__APRIL 17, 2010

Case Report # 3

- 26 yr old male with snake envenomation and signs of pulmonary edema
  - Pulmonary oedema complicating snake bite due to *Bungarus caeruleus (common krait):* Singapore Med J C a s e R e p o r t 2007; 48(8) : e227

Case Report # 4

- 40 yr old jordanian man with h/o snake bite develops acute mi
  - *Am. J. Trop. Med. Hyg., 64(5, 6), 2001, pp. 280–282* Copyright 2001 by The American Society of Tropical Medicine and Hygiene

Case Report # 5

- 6 yr old girl presents with flaccid quadriparesis, respiratory failure folowing snake bite @ night
- In 4hrs, pt gradually deteriorated
- Areflexic, unresponsive pupils, loss of brain stem reflexes
- ASV started, recovered after 48 hrs
  - *Snake bite mimicking brain death: Cases Journal* 2008, **1:**16doi:10.1186/1757-1626-1-16

Plasmapheresis in Snake Envenomation

Plasmapheresis

1. Plasmapheresis is used as an adjuvant treatment in Snake envenomation
2. Decreases Venom induced toxicity
3. Relieve from complications
4. Reduces prolonged hospital stay

Venomus species in Turkey mainly belong to the family of Acrochordidae, Viperidae, Elapidae and Colubridae. *

*Macrovipera lebetina**	(Levantine Viper, Koca Engerek [in Turk.]),
Montivipera xanthina	(Ottoman Viper, Turkish Viper, Seritli Engerek[in Turk]),
Montivipera raddei	(Radde's Viper, Armenian Viper, Agri Engeregi [in Turk]),
Montivipera wagneri	(Wagner's Viper, Wagner Engeregi [in Turk.]),
Montivipera albizona	(Central Turkish Mountain Viper),
Montivipera bulgardaghica	(BolkarDagh Viper, Bolkar Engeregi [in Turk.]),
Vipera ammodytes	(Horned Viper, Sand Viper, Boynuzlu Engerek [in Turk.]),
Vipera transcaucasiana	(Transcaucasian Sand Viper),
Vipera (Pelias) barani	(Baran Engere?i – Baran's Adder),
Vipera (Pelias) kaznakovi	(Çoruh Engere?i – Pontic Adder),
Vipera (Acridophaga) anatolica	
Vipera (Acridophaga) eriwanensis	
*Walterinnesia morgani**	(Desert Black Cobra *Vipera (Pelias) pontica*
Malpolon monspessulanus	(Montpellier Snake, Çukur Basli Yilan [in Turk.])

- Cesaretli Y, Ozkan O. Scorpion stings in Turkey: epidemiological and clinical aspects between the years 1995 and 2004. *Rev Inst Med Trop Sao Paulo*. 2010;52(4):215–220. doi:10.1590/S1678-91992010000400007.

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Indications for Antivenin Therapy.

1. Impaired consciousness.
2. Neurotoxicity.
3. Abnormal EKG, hypotension and shock.
4. Homeostatic abnormalities. (spontaneous systemic bleedings and coagulopathy)
5. Generalized rhabdomyolysis.
6. Evidence of severe intravascular hemolysis.
7. Evidence of renal failure such as uremia, oliguria or anuria.

- Ertem K. Venomous snake bite in Turkey: First aid and treatment. *Eur J Gen Med*. 2004;1(4):1–6. http://dergipark.ulakbim.gov.tr/ejgm/article/view/5000115184.
- Cesaretli Y, Ozkan O. Scorpion stings in Turkey: epidemiological and clinical aspects between the years 1995 and 2004. *Rev Inst Med Trop Sao Paulo*. 2010;52(4):215–220. doi:10.1590/S167891992010000400007.

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Grade	Degree of Envenomation	Signs and symptoms	Initial dose of antivenom
0	None	None	None
1	Mild	Mild to moderate pain. Edema 4 – 5 inches from bite site in first 12 hours. No Systemic signs of envenomation. No Laboratory abnormalities.	4 – 5 vials
2	Moderate to severe.	Severe pain. Edema 6 – 12 inches or more in first 12 hours after bite. Nausea vomiting, diplopia, perioral paresthesia. and other laboratory anomalies.	10 – 15 vials
3	Severe to very severe	Very severe pain. Edema rapidly extending to trunk. Severe systemic signs. Severe laboratory anomalies.	15 – 20 vials

- Ertem K. Venomous snake bite in Turkey: First aid and treatment. *Eur J Gen Med*. 2004;1(4):1–6. http://dergipark.ulakbim.gov.tr/ejgm/article/view/5000115184.
- Cesaretli Y, Ozkan O. Scorpion stings in Turkey: epidemiological and clinical aspects between the years 1995 and 2004. *Rev Inst Med Trop Sao Paulo*. 2010;52(4):215–220. doi:10.1590/S16789199201000040007.

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“European Viper Venom®” (Intervax Biological Ltd., Toronto, Zagreb, Croatia)

“Pasteur Ipser Europe®” (Pasteur Merieux, Lyon, France)

“Polyvalent Snake Venom Antiserum®” (Vacsera, Giza, Egypt)

“CroFab” (Savage Laboratories Melville, NY)

- Sönmez BM. Clinical Aspects and Emergent Management of Snake Bites Presented to Emergency Department. *J Clin Anal Med*. 2015;6(5). doi:10.4328/JCAM.2253.
- Ertem K. Venomous snake bite in Turkey: First aid and treatment. *Eur J Gen Med*. 2004;1(4):1–6. http://dergipark.ulakbim.gov.tr/ejgm/article/view/5000115184.

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Take Home Message

1. Anti-Snake Venom when it is indicated
2. Anti-Snake Venom has got its own Side Effects
3. Neostigmine and Glycopyrrolate or Atropine to neutralize the Non depolarization muscle relaxant effect in Cobra Envenomation
4. Krait Envenomation is mostly presynaptic and if axonal damage occurs Anti-Snake Venom is of no use
5. Mechanical Ventilation in Ventilatory failure in Elapid Bites

Take Home Message

1. Renal Replacement Therapy in Viper Envenomation
2. Fresh Whole Blood for & Blood Products for Venom Induced Consumption Coagulopathy
3. Identifying Early Sepsis (ISE) and Early Goal Directed Therapy in Sepsis
4. Plasmapheresis will become the First Line of Treatment in Snake Envenomation

Thank You

Dr T. S. Srinath Kumar