# Snake bite induced sepsis with multi organ failure successfully treated with Extracorporeal Cytokine Adsorption Device (ECAD) therapy along with standard of care - a case series

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***ABSTRACT — OBJECTIVE:*** *According to WHO, snake bite is one of the most important Neglected Tropical Diseases (NTD) (in 2017 again) in terms of both incidence, severity and high mortality, challenges being the shortage and affordability of anti-venom. We reported two cases of patients complaining of pain and swelling due to snake bite.*

*DISCUSSION: Snake venoms stimulate the activation of mast cells which lead to histamine release, inducing vascular permeability and vasodilatation leading to extravasation. In the present cases, the patients presented with local pain and swelling. Disseminated Intravascular Coagulation (DIC) was observed along with Acute Kidney Injury (AKI).*

*CONCLUSIONS: Extracorporeal cytokine adsorption device along with standard of care seems to be a promising and safe treatment modality to stabilize and recover snake bite envenomation induced complications leading to shorter ICU stays and better survival.*

***KEYWORDS***
*Envenomation, Sepsis, Acute Kidney Injury, Disseminated Intravascular Coagulation, Cytosorb.*

## INTRODUCTION

According to WHO, snake bite is one of the most important Neglected Tropical Diseases (NTD) (in 2017) in terms of both incidence, severity and high mortality[1], challenges being the shortage and affordability of anti-venom. At the same time other contributory factors being, unpredictable process of neutralization of venom despite adequate antivenom, unpredictable inflammatory response and venom-F(ab) complexes precipitating AKI. Snakes represent the most venomous animals; their venoms are complex mixtures of molecules that induce diverse effects on the humans, which are characterized by local tissue damage involving hemorrhage, blistering, myonecrosis and inflammation. The inflammatory response has relevance in the evolution of tissue damage; it is associated with edema, pain, leukocyte infiltration and release of several mediators. Pathogenesis induced by snake venoms is multi-factorial and complex; it is characterized by local and systemic alterations[2,3]. Several studies[4-7] involving animal models have demonstrated release of interleukin-6 (IL-6), nitric oxide (NO), IL-5, tumor necrosis factor-a (TNFa), IL-4, IL-10, prostaglandins and leukotrienes, with distinct time courses in production post venom exposure

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for individual mediators. Cytokine release induces cytokine production and re-release, which in turn aggravates cell and organ damage and may lead to an ongoing vicious circle which is also known as "cytokine storm"[8]. The extracorporeal cytokine haemadsorption device (ECAD) "Cytosorb®" (Cytosorbents Corporation, Monmouth Junction, NJ, USA) has been designed to directly capture and reduce mid-molecular weight inflammatory mediators (~10-60 kDa) which are vital players in clinically complex manifestations. Therefore, we present a "duplet" of vasculotoxic snake bite envenomation treated with novel ECAD therapy along with standard of care with successful outcomes.

## CASE 1

A 66 year old male, who suffered vasculotoxic snake bite was admitted to a local hospital complaining of right lower limb swelling and breathlessness to which he received an Anti Snake Venom (ASV) along with analgesics. Further, he became anuric, required intubation and ventilation before shifting to the ICU of Ruby Hall Clinic (RHC). Upon admission the APACHE II and SOFA scores were 27 and 11, respectively (predicted mortality: 60.5%). The patient was afebrile, anuric, on 0.4 FiO2, PEEP of 5 with bilateral crepitations on auscultation while chest x-ray showed pulmonary edema. The patient did not require ionotropes with MAP of 90 mm Hg. Except ptosis, no other significant neurological signs were observed. IL 6 levels were found to be 112.3 pg/ml, CRP: 11.0 mg/dL and total creatinine kinase (CK) levels: 28895 U/L. Thromboelastogram (TEG) was suggestive of severe fibrinolysis and delayed clotting while PT was 17.9, INR: 1.60, Platelet count: 60,000/mcl, and WBC count: 38,500 with 91% neutrophilia. Treatment started with 10 vials of ASV along with intravenous clindamycin and metronidazole. Progressively, two Cytosorb devices were used on Day 1 and Day 3 due to over whelming inflammatory status, each running for 12 hours without anticoagulants. Post Cytosorb therapy, IL6 levels plummeted along with APACHE II and SOFA scores (Table 1 and Table 2). In the first week, he was dialyzed on every alternate day and required bedside debridement and dressing. Enterococcus fecalis was found from his blood culture for which he received vancomycin. Patient remained in the ICU for 12 days of which 7 days on ventilator. Finally he was extubated on day 8 and was discharged from the hospital after 18 days of stay.

**Table I.** Cytokine levels (in picogram/mL unit).

| | IL6 | IL 10 | IL1 | TNF alpha |
|---|---|---|---|---|
| Before 1st Cytosorb | 112.3 | – | – | – |
| Post 1st Cytosorb | 92.3 | 1.28 | 3.68 | 0.0 |
| Post 2nd Cytosorb | 21.12 | 0.0 | 3.68 | 0.0 |

**Table II.** APACHE II and SOFA scores.

| | APACHE II | SOFA | Predicted mortality (%) |
|---|---|---|---|
| Before 1st Cytosorb | 27 | 11 | 60.5 |
| Post 1st Cytosorb | 17 | 10 | 26.2 |
| Post 2nd Cytosorb | 12 | 9 | 21 |

## CASE 2

Another interesting case of 55 yrs old male, complaining of pain and swelling from right heel (the site of bite) to groin due to snake bite. Prima facie, he was taken to the local hospital where he received primary care and ASV. Thereafter, he was brought to RHC and on examination; no history of bleeding from bite site or any other site, ptosis, breathlessness and vomiting or abdominal pain were reported. On admission, the patient was afebrile and was given Tramadol and Paracetamol as non-nephrotoxic analgesia with heart rate of 75 bpm; blood pressure: 104/67, respiratory rate: 22 breaths/min and maintaining well on room air. Prothrombin time was calculated to be 17 sec, metabolic acidosis was diagnosed on ABG evaluation, IL6 levels were found to be 59.7pg/ml, CRP: 8.5mg/dL, APACHE II and SOFA score were 4 and 2, respectively. Hemogram was abnormal with hemoglobin of 9.4g/dL, WBC count was 19,500 cells/mcl and platelet count to be 1,35,000/mcl. The creatinine kinase value on admission was 2691 U/L and the right lower limb was in impending state of compartment syndrome with probably myonecrosis setting in leading to circulatory shock. He was immediately started on 4 vials of ASV in 500 ml NS every 6 hours followed by ulcer prophylaxis and Piperacillin + Tazobactam by IV route. Intake of fluids and urine output were monitored. Elevated inflammatory response was observed (IL6 59.7 pg/ml, CRP 8.5 mg/dL); thereby, it was considered to use Cytosorb as well as debridement of right lower limb. A total of two cartridges of Cytosorb were used continually for 12 hours each. Further, in view of feeble distal pulsations on the site of snake bite, a decision for fasciotomy was taken and underwent the procedure successfully. After the cytokine removal therapy and the surgical procedure, the patient gradually became afebrile and clinically stable. ASV was continued at the earlier

dose and was additionally transfused with 2 pints of Fresh Frozen Plasma (FFP) and 1 pint of PCV. PT INR was normalized and Renal Function Test (RFT) remained normal and eventually ASV was discontinued on day 6; transfusions were stopped as hemogram significantly improved with hemoglobin 10.9 g/dL, WBC count 12,700 cells/mcl and platelet count was noted to be 2,43,000/mcl. IL6 levels came down to 51.3 pg/ml. PT INR remained normal and therefore the patient was shifted out of the critical care unit. The dressing of fasciotomy site was carried out over next 5 days. The patient was comfortably monitored in the ward and was successfully discharged on day 11. Total duration of hospital stay was 10 days out of which he stayed in ICU for 5 days.

## DISCUSSION

Most of the literature is focused on high mortality engendered by snake bite. However, in those patients who survive the initial few hours suffer from local and systemic complications. These may be due to the direct toxicological action of the venom on distant organs with or without iatrogenic manipulations. Some enzymes in the snake venom induce local tissue destruction, resulting in different levels of necrosis[9]. With respect to multi organ failure, endothelial cell injury, oedema formation, sequestration, excessive systemic host inflammatory response are largely mediated by complex immunological processes, turning protective mechanism into poorly regulated immune response through maladaptive release of endogenously generated mediators[4]. Involvement of inflammatory process in the pathogenesis of snake envenomation was reported since 90 s [10-12]. Increase of capillary permeability was reported after snake envenomation leading to the release of several mediators. Many components of snake venoms (PLA2s, bioamines and proteinases) contribute to the induced inflammatory response, which is initiated by an increase of vascular permeability followed by cell infiltration. Further activation of the complement system results in the formation of many additional degradation products that serve as important mediators of inflammation. Snake venoms stimulate the activation of mast cells which lead to histamine release, inducing vascular permeability and vasodilatation leading to extravasation. In the present cases, the patients presented with local pain and swelling. Disseminated Intravascular Coagulation (DIC) was observed along with Acute Kidney Injury (AKI). Generally, coagulation abnormalities (coagulopathy) are characterized by a prolonged activated partial thromboplastin time, prothrombin time and thrombin time, which were clearly observed in the above cases. Moreover, activated platelets release a number of mediators and cytokines from stores within their α and dense-granules for further platelet recruitment, activation and aggregation further leading to neutrophil intravascular crawling and transmigration and the initiation of inflammation[13]. Such platelet-neutrophil aggregates contribute to a variety of inflammatory settings, including acute lung injury, acute kidney injury, sepsis and atherosclerosis[14-16]. Occlusion of renal vessels by microthrombi as well as glomerular damage by the immune complexes of venom and F(ab) of antivenom could be the attributing factor for AKI along with hemoglobinuria and myoglobinuria which causes nephrotoxicity. Coagulopathy and AKI must have synergistically fueled the vicious cycle of cytokine storm and that is why Cytosorb was seen as a suitable option along with standard of care in order to expedite the recovery process. This is the first case series reported to the best of our knowledge where an Extracorporeal Cytokine Adsorption Device (ECAD) has been used in snake bite envenomation. Due to limited literature available pertaining to the use of cytokine adsorber in this domain, larger prospective studies are required to evaluate the exact utility in such severe and complex conditions.

## CONCLUSIONS

Extracorporeal cytokine adsorption device along with standard of care seems to be a promising and safe treatment modality to stabilize and recover snake bite envenomation induced complications leading to shorter ICU stays and better survival.

**Conflicts of interest:**
The Authors declare that they have no conflict of interests.

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