# A CLINICAL EXPERIENCE OF USING EXTRACORPOREAL CYTOKINE ADSORPTION DEVICE (CYTOSORB®) IN A CASE OF DENGUE FEVER

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**ABSTRACT**

**BACKGROUND**

Dengue is a mosquito-borne viral disease transmitted by *Aedes aegypti* and *Aedes albopictus*. It is hypothesised that elevated cytokines such as tumour necrosis factor alpha (TNF-α), interleukins and interferon gamma (IFN-γ) during severe dengue causes damage to the endothelial cells of the capillaries that results in fluid leakage. A novel Extracorporeal Cytokine Adsorption Device (ECAD) CytoSorb® targets the cytokines helps modulate immune response and prevent multiorgan dysfunction syndrome.

**MATERIALS AND METHODS**

We report a case of dengue fever with septic shock and multiorgan failure admitted in the intensive care. He was treated with standard of care along with mechanical ventilation and renal replacement therapy. A novel ECAD CytoSorb was used as an adjuvant supportive therapy. The patient also received multiple transfusions to address thrombocytopenia and coagulopathy.

**RESULTS**

The patient showed gradual improvement. The patient showed normalised central nervous system function, improved oxygenation status, adequate renal function and normal platelet count at the time of discharge. The liver function had also improved significantly.

**CONCLUSION**

Extracorporeal Cytokine Adsorption device CytoSorb® might be useful option as an adjuvant therapy in dengue patients with MODS.

**KEYWORDS**

CytoSorb®, Dengue Fever, Multiorgan Failure Syndrome.

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## BACKGROUND

Dengue is a mosquito-borne viral disease transmitted by *Aedes aegypti* and *Aedes albopictus*. Around 2.5 billion people at risk of dengue with an annual range of 50 to 390 million infections including dengue fever, Dengue Haemorrhagic Fever (DHF) and Dengue Shock Syndrome (DSS).[1] It is hypothesised that elevated cytokines such as Tumour Necrosis Factor Alpha (TNF-α), Interleukin (IL) and interferon gamma (IFN-γ) during severe dengue causes damage to the endothelial cells of the capillaries that results in fluid leakage.[2] Currently, no vaccine or any specific medicine is available to treat dengue;[3] although, steroids and immunoglobulins have shown evidence-based benefits.[4] A novel Extracorporeal Cytokine Adsorption Device (ECAD) CytoSorb® (CytoSorbents Corporation, USA) targets cytokines, helps modulate immune response and prevent Multiorgan Dysfunction Syndrome (MODS).

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Here, we report a case of dengue fever with MODS treated with standard of care along with ECAD (CytoSorb®).

### Case Presentation

A 32-year old male patient was admitted to a tertiary care hospital on December 3, 2014, with presenting symptoms of fever, chills, dyspnoea, yellow discoloration of skin and sclera. He was diagnosed as suffering from dengue fever after his serological tests were positive to dengue virus. Over the next seven days, his condition progressively worsened. He was referred to Noble Hospital on December 11, 2014, with progressively worsening multiorgan failure state. At the time of admission, the patient fulfilled the diagnostic criteria for Systemic Inflammatory Response Syndrome (SIRS) (body temperature- 100°C, heart rate- 120-130 bpm, respiratory rate- 26-30 breaths/min. and leucocytosis- 16400) along with acute organ dysfunction (brain agitation, thrombocytopenia, hypoxia, kidney dysfunction, metabolic acidosis and arterial hypotension), sepsis and septic shock. His APACHE score at admission was 27. He was being managed in ICU. Within 24 hrs. of admission, the patient required mechanical ventilator support in view of worsening Acute Respiratory Distress Syndrome (ARDS) and resulting hypoxia. He was treated with standard of care that included optimisation of fluid status, nutritional support, antibiotics, proton pump inhibitors, treatments for hepatic

encephalopathy, blood products and other standard supportive care.

ECAD (CytoSorb®) was added as a supportive therapy as the patient showed evidence of SIRS with MODS. He was given three cycles of ECAD with CytoSorb® along with renal replacement therapy on day 2, 4 and 6 of admission. The duration of each session was six hours with blood flow rate of 250 mL/min. The sessions were heparin free (Table 1). There was no major complication during or after the CytoSorb® therapy except mild irritability of patient that settled with sedatives. The patient showed gradual improvement. His APACHE score after third cycle of CytoSorb® therapy was 12. The patient was shifted out of ICU on day 13 and subsequently discharged. At the time of discharge, he had normalised central nervous system function, improved oxygenation status, adequate renal function and normal platelet count. The liver function had improved significantly and he was fully ambulatory. The clinical and laboratory parameters before and after CytoSorb® device treatment are given in Table 2 and Table 3.

| | **Treatment 1** | **Treatment 2** | **Treatment 3** |
|---|---|---|---|
| Duration (hrs.) | 6 | 6 | 6 |
| Blood Flow Rate (mL/min.) | 250 | 250 | 250 |
| Blood Pressure (BP) (mmHg) | 130/80 | 126/82 | 138/74 |
| Pulse Rate (PR) | 110 | 122 | 118 |
| Respiratory Rate (RR) | 30 | 22 | 24 |

***Table 1. Three Cycles of CytoSorb Treatment***

| **Parameters** | **Before CytoSorb Treatment** | **After CytoSorb Treatment** |
|---|---|---|
| APACHE score | 27 | 12 |
| Chronic organ dysfunction | No | No |
| ARF | Yes | No |
| Temperature (°F) | 100 | 99.8 |
| Heart rate (bpm) | 140 | 100 |
| Respiratory rate breaths/min. | 26-28 | 20-26 |
| Sodium (mEq/L) | 138 | 135 |
| Potassium (mEq/dL) | 3.9 | 3.6 |
| Creatinine (mg/dL) | 3.96 | 1.59 |
| Haematocrit | 27.7% | 26.7% |
| Leucocytes | $16.3 \times 10^3$ | $13.2 \times 10^3$ |
| Platelets (per mcL) | 50000 | 311000 |
| GCS | 9 | >10 |
| Mean arterial pressure (mmHg) | 84 | 104 |
| aPTT (sec.) | 43 | >60 |
| SGOT (U/L) | 15690 | 156 |
| SGPT(U/L) | 3910 | 84 |
| Serum Lactate | 6.7 | 1.9 |

***Table 2. Clinical and Laboratory Examination of the Patient Before and After the Treatment***

ARF - Acute Renal Failure, GCS - Glasgow Coma Scale, aPTT - Activated Partial Thromboplastin Time, SGOT - Serum Glutamic Oxaloacetic Transaminase, SGPT - Serum Glutamic Pyruvic Transaminase.

| **Parameters** | **Before** | **After** |
|---|---|---|
| pH | 7.2 | 7.4 |
| $PaCO_2$ (mmHg) | 28 | 34 |
| $PaO_2$ (mmHg) | 37 | 215 |
| SBC (mmol/L) | 15 | 22.9 |
| $O_2$ Saturation | 63% | 120% |
| (A-a) $O_2$ gradient (mmHg) | 281.6 | 98 |
| Base Excess | -13 | -1 |

***Table 3. Arterial Blood Gases Value Before and after CytoSorb Therapy***

$PaCO_2$ - Partial Pressure of Carbon Dioxide, $PaO_2$ - Partial Pressure of Oxygen, SBC - Standard Bicarbonate, (A-a) $O_2$ - Alveolar-arterial oxygen.

**DISCUSSION**

Dengue is a febrile illness that in severe cases may have fatal outcome. The exact pathophysiology is still unknown and it is observed that host immune system, host genetic makeup and pathogen virulence are responsible for rapid deterioration in patients with dengue.[4] Our patient was diagnosed with dengue fever, had SIRS, ARDS and hepatic encephalopathy. A total of three cycles of CytoSorb® therapy was given to the patient along with supportive treatments. The patient's clinical condition gradually improved. We observed that treatment with standard of care along with ECAD as a supportive therapy helped to stabilise a dengue fever patient with MODS.

Several circulating cells are activated during high viral burden. During dengue fever, high levels of cellular activation maybe harmful to the host. It is observed that at later phase of the disease, effectors memory cells (TEM) are also activated. In response to infectious pathogens, TEM cells shows immediate effector function and secretes IL-2, IFN γ and other cytokines.[5,6] CytoSorb® therapy modulates the immune response through eliminating high cytokine levels.[7] The CytoSorb device is a relatively simple haemadsorption column consisting of polystyrene divinylbenzene copolymer beads, which are highly porous and covered with a biocompatible polyvinylpyrrolidone coating. The CytoSorb® polymer beads facilitate a

concentration-dependent and size-selective removal of molecules with middle molecular weight of approximately 10-50 kDa.

The cytokines adhere through hydrophobic interactions with the neutral lipophilic surface of the polymer, while essential blood proteins of larger size such as albumin are passed back to the patient through the filter.[8] Schadler *et al* conducted a randomised controlled study of a cytokine haemadsorption device in septic patients with acute lung injury. CytoSorb® was well-tolerated and a significant reduction in cytokines was observed.[9] In a recent study by Basu *et al*, a 36-year-old female patient with septic shock and multiorgan failure was well treated with standard care and CytoSorb® as an adjuvant therapy.[10] In our case, CytoSorb device was added as a supportive therapy to address underlying pathology due to cytokine storm. The device helped to stabilise and revive the dengue patient with MODS and shock. Majority of laboratory parameters were within the normal range after the therapy and no major adverse events were reported during or after the CytoSorb therapy. To the best of our knowledge, this case is the first report on clinical application of CytoSorb haemadsorption in a case of dengue fever with MODS treated successfully with standard of care along with ECAD (CytoSorb®).

## CONCLUSION

CytoSorb® seems to be an interesting and safe extracorporeal therapy option to stabilise and help dengue patients with MODS to recover. However, further research is warranted in a larger pool of patients to understand the clinical role of this device in the management of dengue fever.

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