# CytoSorb
# Study Proposal

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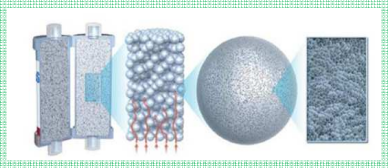
## Introduction

Sepsis is the leading cause of morbidity and mortality in critically ill patients.
Mortality is higher when associated with acute kidney injury (AKI) and in continuous renal replacement therapy (CRRT).
The mechanisms of sepsis-induced tissue injury seem to be related to the ischemic response to hypoperfusion, but also to a direct detrimental activity induced by circulating mediators. These factors interact in a dynamic network to induce multiple organ failure.
Extracorporeal techniques for purifying blood have been developed as systemic therapies for the treatment of sepsis and septic shock.
The main extracorporeal therapies that can be prescribed to reduce cytokines levels in blood are:

- hemoperfusion
- high Volume Hemofiltration (with high flux membranes)
- therapies with high cut-off membranes
- coupled plasma filtration adsorption (CPFA)
- plasmapheresis

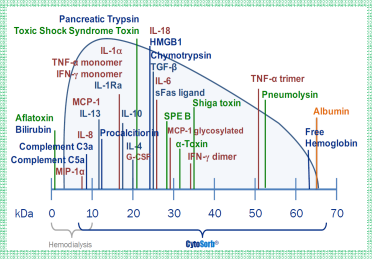
CytoSorb™ (Aferitica, Mirandola (Mo), Italy) cartridge is applied in hemoperfusion modality and contains 10 grams of polystyrene divinyl benzene copolymer beads with a biocompatible polyvinylpyrrolidone (PVP) coating.
The representative structure is as follow:

The characteristics of the cartridge are described in the following table:

| | |
|---|---|
| **Extracorporeal blood volume:** | 120 ml |
| **Blood flow rates min-max:** | 100-400 ml/min |
| **Max. treatment duration:** | 24 hours |
| **Anticoagulation:** | heparin or citrate |
| **Sterilization:** | gamma sterilization |

Different studies in literature have already verified both *in vitro* and *in vivo* the removal capacity of different cytokines and other molecules with Cytosorb.




The CytoSorb treatment has demonstrated to be efficient in the removal of inflammatory cytokines such as Tumor Necrosis Factor alpha (TNF-α) and Interleukin-6 (IL-6), but not Interleukin-10 (IL-10).
This poster describes the rational and the clinical protocol to further characterize *in vivo* the new cartridge efficiency in septic shock patients treatment.

## Aim of the study

The aim of this investigation is a randomized, controlled, pilot, clinical study in 6 septic shock patients in extracorporeal hemoperfusion with CytoSorb cartridge. It will evaluate the therapy effects on:

- *in vivo* removal of sepsis mediators
- *in vitro* reduction of apoptosis on cell cultures

Furthermore, we aim to evaluate apoptotic effect of septic patients' plasma taken before and after CytoSorb cartridge, at different time points.

## Primary Endpoints

*In vivo* evaluation of the cartridge in terms of removal capacity of plasma levels of the following molecules:

- pro-inflammatory
  - *Interleukin-1β*
  - *Interleukin-6*
  - *TNF-α*
  - *Angiopoitin-2*
- anti-inflammatory
  - *Interleukin-10*
  - *Angiopoietin-1*

## Secondary Endpoints

*In vitro* evaluation of the effect of patients plasma sampled before and after 24 hours of treatment with CytoSorb, on monocytes cell line U937 and on Renal Tubular Cells incubated for 24 hours.

### Inclusion Criteria:

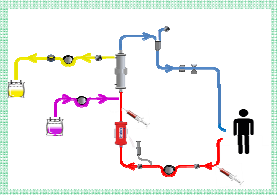
- presence of septic shock in accordance to the criteria defined by the American College of Chest Physicians and by the Society of Critical Care Medicine
- presence of AKI determined by the evaluation of serum creatinine or urinary output (inclusion in the failure group of RIFLE criteria)
- decision to start and to continue the treatment for at least 24 hours

### Exclusion Criteria:

- age lower than 18 years
- solid organ or bone marrow transplantation, hemorrhagic dysfunction, thrombophilia, chronic renal failure, glomerulonephritis or collagenopathies based on clinical evaluation
- pregnancy
- autoimmune diseases in immunosuppressive therapy or immunodepressed patients
- transplanted patient in immunosuppressive therapy
- regional anticoagulation with citrate
- cardio circulatory arrest (ACC)
- neoplasia in chemotherapy
- life expectation lower than 24 hours

### Therapy and treatment parameters

The treatment will last 24 hours.
The CytoSorb cartridge will be set before the hemofilter of a Continuous Veno-Venous Hemofiltration (CVVH).
The replacement site will be placed after the cartridge and before the hemofilter, as drawn in the figure on the left.



Blood samples will be collected pre- and post-CytoSorb cartridge at every time point.
The time points will be set at 0, 1, 4, 8 hours and post treatment.
5 ml of blood will be collected for each sampling point.
Treatment maximum duration will be 24 hours.
After 24 hours of CytoSorb procedure, the patient will continue the standard therapy based on clinical prescription.
At the end of the study the data will be collected at the International Renal Research Institute of Vicenza (IRRIV).

## Results

The evaluation of the cartridge performances will be assessed by the reduction ratio trend. In particular, the "instantaneous" reduction ratio will be considered as following:

$$R.R. = \frac{Cpre - Cpost}{Cpre}$$

where *Cpre* is the blood concentration of each considered molecule before the cartridge and *Cpost* is the blood concentration of each considered molecule after the cartridge.
A graph *R.R. vs time* will be created in order to estimate the efficiency of the cartridge along the treatment time.