# Use of CytoSorb in the emergency department-high dependency unit: A case report and a mini review

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## Abstract

Circulating inflammatory mediators and cytokines play a pivotal role in the progression of sepsis, leading in turn to septic shock, organ failure and resistance to standard therapy. Blood purification therapies may be adjuvant treatment for severe sepsis, but results have been shown to be so far controversial. Recently, CytoSorb has achieved promising outcomes on reduction of cytokine blood levels, improvement of clinical parameters and mortality in sepsis, as well as in other acute conditions. It is mostly used in Intensive Care Unit (ICU), in isolated hemoperfusion, or inserted in other circuits in addition to Continuous Renal Replacement Therapy (CRRT), heart-lung machines and extracorporeal membrane oxygenation. We report a case of septic shock occurred in our Emergency Department-High Dependency Unit (ED-HDU), resistant to standard therapy and improved after CytoSorb, so avoiding ICU hospitalization.

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### *Highlights*

- *CytoSorb is a rescue therapeutic option for septic shock.*
- *CytoSorb is a safe, simple, well-tolerated, no haemolytic device.*
- *CytoSorb reduces cytokine blood levels in septic shock, so leading to hemodynamic stabilization.*
- *Adequately staffed Emergency Departments-High Dependency Units are decisive to manage critical patients, possibly avoiding Intensive Care Unit (ICU) admission and sparing ICU's resources.*

## Case Report

A 34-years-old woman with lupus nephritis, on chronic therapy with immunosuppressants, was admitted to the Emergency Department (ED) with fever, cough and anuria. Her past medical history revealed previous hospitalizations for lupus nephritis exacerbations with neurological involvement. We started routine diagnostic work-up as follows: blood exams, blood cultures, 12-lead ECG, pulse oximetry, invasive arterial blood pressure measurement, hourly monitoring of diuresis, temperature measurement and gas records. Gas exams showed combined metabolic acidosis and respiratory alkalosis, as expected. Blood exams showed anemia, AKI and high inflammatory indexes with a Sequential Organ Failure Assessment (SOFA) score 8. Severe hypotension, anuria and SOFA score made likely a septic status. An initial ultrasound assessment revealed bilateral pleural effusion, lung A lines predominance and Inferior Vena Cava (IVC) of 2 cm, with respiratory collapsibility of 40%. No significant echocardiographic alterations were found. Hence, immunosuppressants were stopped and therapy with fluids and broad-spectrum antibiotic was started. A chest CT scan was performed showing bilateral pneumonia and blood transfusion was also performed. Oxygen with High Flow Nasal Cannula (HFNC) was also supplied. Due to the persistence of hemodynamic instability, norepinephrine was added to the infusion therapy and diuretic was started. In order to give continuous close monitoring, the patient was moved from ED to our ED-HDU, a

sub-intensive care unit located between Emergency Room (ER) and ICU, with availability of advanced monitoring, non-invasive ventilation and possibility to give vasoactive drugs. After 24 hours, blood cultures were positive for *S. Pneumoniae*. Anuria, hypotension and high inflammation indexes persisted. We potentiated vasopressor support and we considered starting Continuous Veno-Venous Hemodiafiltration (CVVHDF) in order to maintain hydro-electrolytic homeostasis, prevent further renal insult and allow antibiotic therapy without limitations or complications. Taking into account the presence of dialysis devices and nephrology consultants in our ED-HDU, informed consent was obtained from the patient and a femoral Central Venous Catheter (CVC) was implanted. CVVHDF was performed for 48 hours as standalone therapy, using a renal replacement device (Prismaflex- Baxter), with heparin anticoagulation and a blood flow rate of 200 mL/h. After 48 hours from CVVHDF, assuming that the persistence of AKI with anuria and elevated inflammatory markers, above all Procalcitonin (PCT), were possibly related to cytokine storm, CytoSorb cartridge was placed downstream of the blood pump circuit, with a blood flow rate of 200 mL/h. Hence, CytoSorb was not started from the beginning, but only when the balance of clinical status was considered to be tipped towards a cytokine storm. This treatment was conducted intermittently for two consecutive sessions, each lasting 10 hours. Fluid load was closely monitored daily through bedside echo. Between CytoSorb sessions, ultrafiltration in CVVHDF modality was also performed as needed to control fluid homeostasis. The patient tolerated very well the procedure with no side-effects and was transferred to the Unit of Internal Medicine, so avoiding ICU admission. The effect of CVVHDF without CytoSorb consisted of unstable improvement of blood pressure, consequently still requiring norepinephrine infusion, associated with a slight reduction of inflammatory indexes and SOFA score. By contrast, CVVDHF with CytoSorb allowed hemodynamic stabilization with no further norepinephrine demand, associated with CRP, PCT and SOFA score reduction. During the renal replacement treatment, norepinephrine infusion was gradually stopped and the patient preserved a good oxygen saturation with High Flow Nasal Cannula (HFNC), so that mechanical ventilation was not necessary. CytoSorb allowed a reduction of the vasopressor dose and hemodynamic stabilization, with gradual recovery of spontaneous diuresis. The patient was monitored at baseline, at 24, 48 and 72 hours and blood samples were drawn to measure a number of parameters (Table 1).

## Discussion

AKI is one of the most important septic complication representing an independent risk factor for mortality. During septic condition, elevated and imbalanced pro- and anti-inflammatory mediators, coupled with severe endothelial dysfunction and a perturbed coagulation cascade, works synergistically to induce chemically- and biologically-mediated kidney injury. Renal Replacement Therapies (RRTs) have been tested to restore a balanced immune response by clearing/deactivating inflammatory mediators[1] but they have not to date been successful and are not widely utilized in practice, depending on resources and local expertise.[2] Table 2 shows the core differences of the several different purification systems used in sepsis.[2–6] The indications for the use of RRT in sepsis-associated AKI are consistent with those for other causes of AKI but, given the potential confounding effects of sepsis on conventional markers, some investigators have suggested prolonged oliguria as sufficient indication to start RRT. The use of continuous therapies in sepsis-associated AKI are still preferred managing to improve hemodynamic stability, temperature regulation and continuous fluid management. Of note, also the polymer-based sorbents have shown to be effective in restoring immune homeostasis in septic patients.[3] CytoSorb is one of the several sorbents developed and approved in Europe since 2011 for inflammatory mediators removal. It was used for the first time in 2014 in combination with CRRT, to treat septic shock secondary to beta-hemolytic Streptococcus-induced necrotizing fasciitis.[7] Later on, some case series have been reported in the Literature, but its use has not been so far recognized as a mandatory approach to septic shock. Technically simple and biocompatible, CytoSorb can be entered in most circuits and needs little adjustment without adverse effects, avoiding hemolysis. CytoSorb has a surface of about 45,000 $m^2$, wider than that of the others filters, allowing a rapid adsorption of hydrophobic molecules with a molecular weight between 5 and 55 kDa. Hence, CytoSorb is selective for cytokines, leading to a decrease of key cytokines such as IL- 1β, TNF-α, IL-6 and IL-10 both in ICU patients[8,9] and laboratory septic rats.[10] Endotoxins coming from Gram negative bacteria have higher molecular weight (100 kDa), so they are not removed by CytoSorb. The adsorption is concentration-dependent: the higher are the levels of substances in the blood, the faster they are cleared. Literature provides evidence about reduction of high levels of cytokines, mostly IL-6[2,9,11,12] but results are controversial with no decrease in IL-6 plasma levels and no association with mortality,[13] probably due to influence of treatment duration, cytokines' continuous production and their shift from interstitium into blood.[9,14] Moreover, CytoSorb can reduce levels of PCT and CRP[12,15] which have received, above all, a large consensus as being considered sepsis biomarkers.[16] PCT has been considered a biomarker of "cytokine storm": the higher is the value of PCT, the higher are cytokines levels. Despite its reduction determines improvement in clinical parameters,[15] it is difficult to establish a PCT cut-off. Nevertheless, PCT could indicate when to start sorbent therapy, but not to follow the response to therapy itself.[14] Recent studies have shown that CytoSorb can promote hemodynamic stabilization with a reduction of catecholamines demand, increasing short-term survival and reducing mortality predicted by scores.[8,17] Of note, in patients with refractory septic shock, no responder to fluid challenge, vasopressors are important to reach a Mean Arterial Pressure (MAP) ≥ 65 mmHg and guarantee organ perfusion. However, vasopressor load and prolonged titrated therapy may positively correlate with organ ischemia, tachyarrhythmia, metabolic acidosis and renal failure.[18] CytoSorb influences vasopressors need through the control of the exaggerated immune response and the reduction of inflammatory mediators, which typically lead to hemodynamic stability. In turn, patients with high severity of illness and refractory shock are more likely to benefit of sorbent therapy. Improved hemodynamic associated with a reduction in catecholamine requirements has been acknowledged as a relevant endpoint of sorbent therapy.[14,17,19] These results derive from combination between CytoSorb and CRRT, but also from CytoSorb as standalone therapy.[15] Also, it is well recognized that the serum lactate level is helpful in identifying occult shock and in monitoring response to therapy.[8,11,12,20] In turn, recent studies have shown that, in patients treated with CytoSorb, a baseline lactate level of 6-7.5 and above, together with low thrombocytes count, are associated with higher mortality.[17,19] It is necessary keeping in mind that CytoSorb may interfere with drug kinetics (especially that of lipophilic antibiotics), with unwanted effects (*e.g.*, sub-therapeutic antibiotics concentration that may dampen their efficacy). To date, there is scanty information surrounding the

**Table 1. Changes in laboratory and vital parameters.**

| Parameters | O/A | ST | CVVHDF +ST | CytoSorb therapy | | Stop CytoSorb | |
|---|---|---|---|---|---|---|---|
| | | | | $T_0$ | $T_{24}$ | $T_{48}$ | $T_{72}$ |
| BP (mmHg) | 70/35 | 70/40 | 96/65 | 90/60 | 100/70 | 125/70 | 145/95 |
| PCT (ng/mL) | 25.03 | 98.17 | 33.91 | 23.61 | 20.61 | 7.62 | 4.07 |
| CRP (mg/L)(0.0-1.0) | 10.574 | 22.285 | 41.187 | 39.033 | 19.582 | 10.532 | 5.1 |
| WBC ($10^3$/µL) (4.80-10.80) | 4.18 | 4.9 | 9.32 | 13.4 | 17.82 | 14.82 | 15.60 |
| -Ne (%) (40-74) | 88.1 | 88.8 | 93.7 | 95.2 | 91.2 | 86.4 | 86.7 |
| -Li (%) (19-48) | 8.4 | 9.8 | 5.0 | 2.1 | 4.0 | 5.7 | 4.7 |
| -Mo (%) (3.4-9) | 3.0 | 1.1 | 0.8 | 2.6 | 4.7 | 7.8 | 8.4 |
| -Eo (%) (0.5-7) | 0.3 | 0.1 | 0.3 | 0 | 0 | 0 | 0.1 |
| -Ba(%) (0-1.5) | 0.2 | 0.2 | 0.2 | 0.1 | 0.1 | 0.1 | 0.1 |
| eGFR (mL/min/$m^2$) | 28 | 19 | 45 | 70 | 43 | 54 | 58 |
| Serum Urea (mg/dL)(17-43) | 110 | 126 | 63 | - | 76 | 93 | 134 |
| SCr (mg/dL) (0.60-1.10) | 2.22 | 3.08 | 1.52 | 1.06 | 1.59 | 1.31 | 1.24 |
| PT-INR (0.8-1.2) | 1.04 | 1.25 | 1.11 | 0.93 | 0.94 | 0.88 | 0.89 |
| PLT ($10^3$/µL) | 222 | 204 | 243 | 205 | 178 | 142 | 136 |
| APTT (sec)/Ratio (40/1.33) | 33/1.09 | 35/1.18 | 47/1.55 | 46/1.53 | 72/2.39 | 29/0.97 | 40/1.33 |
| Lac (mmol/L) (1.0-1.8) | 2.8 | 2.2 | 1.6 | 1.5 | 1.3 | - | 1.3 |
| SOFA score (<2) | 8 | 7 | 7 | 5 | 3 | - | 2 |

O/A: On Arrival; ST: Standard Therapy; CVVHDF+ ST: Continuous Veno-venous Hemodiafiltration + Standard Therapy; BP: Blood Pressure; PCT: Procalcitonin; CRP: C-Reactive Protein; WBC: white blood cells; Ne: Neutrophils; Ly: Lymphocytes; Mo: Monocytes; Eo: Eosinophils; Ba: Basophils; eGFR: Estimated Glomerular Filtration Rate; SCr: Serum Creatinine; PT-INR: Prothrombin Time International Normalized Ratio; PLT: Platelets; APTT: Activated Partial Thromboplastin Time; Lac: Lactate; SOFA: Sequential Organ Failure Assessment.

**Table 2. Core differences of several blood purification therapies used in sepsis.**

| | IRRT | CRRT: CVVH, CVVHD, CVVHDF, SCUF, HP, hybrid CPFA, PEX |
|---|---|---|
| **Mechanism** | Diffusive transport (HD) or convection (HF, HVHF) or both (HDF)<br>Presence of a dialysate | • Mainly Convective /Ultrafiltration transport (except for CVVHD diffusion and CVVHDF combination of convection and diffusion). Presence of sterile replacement solution (not for CVVHD and SCUF).<br>• Adsorption of blood (HP) or combination of convective with plasma filtration and adsorption (CPFA)<br>• Filtration with reinfusion of albumin or fresh frozen plasma (PEX) |
| **Effect** | Clearance for small molecular weight solutes and fluids | Clearance for small and middle molecular weight solutes and fluids (CVVHDF). Only fluids for SCUF.<br>Cytokines or poisons or other toxins removal depending on the sorbent (HP): CytoSorb: pro and anti-inflammatory cytokines removal except of endotoxins; Polimixine B: endotoxins removal; Alteco: LPS adsorber; oXiris: endotoxins removal<br>Pathological substances (cytokines, autoantibodies, toxins, abnormal proteins) removal (PEX) |
| **Fluid removal** | Rapid | • CVVHDF: slow<br>• Sorbents: not rely on fluids removal |

**Table 2. Core differences of several blood purification therapies used in sepsis.**

| | | |
|---|---|---|
| | | • PEX: slow large fraction of plasma filtration |
| **Flow rate** | High (up to 500 mL/min) | Low and constant (50-200 mL/min). High intensity dialysis (40 mg/kg/h) does not change the mortality compared to a less intensive treatment (20 mg/kg/h) |
| **Hypotension** | High risk | Present but lower risk |
| **Complexity** | Low | High |
| **Systemic Anticoagulation** | Not necessary | Present (heparin or citrate) |
| **Disadvantages** | Frequent hypotension, arrythmia, hypertension, hyperkalemia | • CVVHDF: filter clotting, air embolism, hypothermia, bleeding, drug levels alteration, prolonged immobilization, hypotension (less frequent than IRRT)<br>• Sorbents: drug kinetic interference, transient thrombocytopenia and leucopenia<br>• PEX: vascular access problems, paresthesia, anaphylactoid reaction to replacement fluid, hypotension, nausea, vomiting, thrombocytopenia |
| **Costs** | Low/moderate | High |

IRRT: Intermittent Renal Replacement Therapy; HD: Hemodialysis; HF: Hemofiltration; HDF: Hemodiafiltration; HVHF: High volume hemofiltration; CRRT: Continuous Renal Replacement Therapy; CVVH: Continuous Veno-Venous Hemodialysis; CVVHD: Continuous Veno-Venous Hemofiltration; CVVHDF: Continuous Veno-Venous Hemodiafiltration; SCUF: Slow Continuous Ultrafiltration; HP: Hemoperfusion; CPFA: Coupled plasma filtration absorption; PEX: Plasmaexchange

use of hemadsorption therapies in septic shock, limited to animal studies, case reports, and retrospective observational studies. These data cannot provide clear recommendations for the use of CytoSorb. Further studies should be useful to better define indication to use, timing and therapeutic efficacy of sorbent agents. Actually, sorbent therapy should not be based only on the presence of high biomarkers level, but also on the monitoring of severity of illness (through APACHE and SOFA scores), norepinephrine need, mortality, length of stay and mechanical ventilation.[9,14] In this scenario, it is important to develop a unique assessment to objectively evaluate the most appropriate patient's care in the emergency setting and the impact of clinical interventions.[21] In the context of ED-HDU, SOFA score has shown promising results in terms of prognostic value, response to therapeutic intervention and discrimination ability for HDU mortality and indication to ICU admission.[22,23] Moreover, additional modified indexes such as qSOFA (Quick Sequential Organ Failure Assessment) and LqSOFA (blood lactate levels + qSOFA) resulted to be useful in predicting, with high sensitivity and specificity, mortality in septic patients, when calculated on admission to ED.[24]

## Conclusions

To the best of our knowledge, there is no previous experience in the use of CytoSorb in an ED-HDU and this is the novelty of the present clinical case. We believe that the presence of ED-HDU with dialysis device has been a winner strategy to manage our patient in the context of sub-intensive care, avoiding ICU admission. In life-threatening conditions like septic shock, RRT is usually under the domain of ICUs.[8,11] Hence, the management of critically ill patients is considered a synonymous of ICU's expertise, but relevant therapy in ED may improve mortality scores and physiologic assessment prior to ICU admission. Therefore, length of stay in ED is often prolonged because of lack of ICU beds, ED overcrowding, ageing population, complexity of some chronic conditions leading to time-dependent complications and increase of mortality scores. Even better, the efficacy of ED intervention may result in avoiding ICU admission and sparing ICU's resources. Hence, ED must be staffed and organized adequately to manage stabilization procedures.[25,26] This case report strengthens the effectiveness of approaching patients with septic shock in the emergency department not only as first aid but as conclusive therapeutic strategy, whenever possible. We believe that the quality of assistance provided during acute management significantly inhibits the progression of organ failure and death, irrespective of patients' location. Waiting for ICU admission without adequate resuscitation strategy may cause dramatic complications leading to death. On the other side, ICU mortality and ICU related long-term complications are documented, mostly due to infections, mechanical ventilation or premature discharge due to beds pressure.[27] Lastly, this manuscript may encourage the use of CytoSorb, when indicated, during the acute phase of medical care, because it is a safe, promising and well tolerated rescue therapeutic option in septic shock.

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