

# Our Four Years Experience of Hemoadsorption, Albumin and Heparin Treatment for Paediatric Sepsis: Let's Give a Chance in Multifactorial Pathological Conditions

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**Abstract:** Extracorporeal blood purification therapies are increasingly applied in the field of intensive care medicine. These techniques are applied to a relevant number of clinical situations as Sepsis, Trauma, burns, Influenza, surgery, Pancreatitis, ARDS, Life support, Liver failure. Compared to filtration-based methods mainly used for renal replacement therapy, newest adsorptive approaches have shown to specifically target the inflammatory cascade by the effective removal of relevant mediators. In the neonatal and pediatric setting however, the application of these methods brings with it various challenges but also profound technical difficulties. Recently, a promising extracorporeal device for cytokine adsorption (Cytosorb) has been introduced, however data for its application in critically ill pediatric patients remains sparse [1]. The lack of data and procedure protocols led us to take some aprioristic diagnostic and speculative decisions only from a scientific point of view: “*in primis*” when we decided for the first time in a pediatric patient to use this “Cytosorb Absorber”, a device not registered and delivered for toddlers; second when it was clear that we could extend its use to not conventional disease therapeutic strategies; third when we decided to give to “Cytosorb” use the appellation and indication of “rescue treatment”. These results are interesting for the scientific community, but further research is needed.

**Keywords:** CRRT, Apheresis, Cytosorb, MOF, Sepsis, Albumin, ECMO

## 1. Introduction

We describe the use of Cytosorb in combination with standard therapy, continuous renal replacement therapy (CRRT) and plasmapheresis in 20 severely ill pediatric patients with multiple organ failure of various etiologies.

This is a historical report of our clinical decisions pathway and of the changes we made in the applicative utilization of Cytosorb during a period of 4 years with particular attention to the story of patient cases that we consider as a turning point that supported our therapeutic strategy changes (Figure 1) [1].

### 1.1. Methodology

The lack of data and procedure protocols related to this new promising extracorporeal device led us to take some aprioristic diagnostic and speculative decisions only from a scientific point of view.

Only after a long period of study, we decided for the first time in a pediatric patient to use this "Cytosorb Absorber", a device not registered or delivered for toddlers.

Only after we decided to give to "Cytosorb" use the appellation and indication of "rescue treatment", we used this device as not conventional disease therapeutic strategies.

Compared to filtration-based methods mainly used for renal replacement therapy, newest adsorptive approaches have shown to specifically target the inflammatory cascade by the effective removal of relevant mediators. In the neonatal and pediatric setting however, the application of these methods brings with it various challenges but also profound technical difficulties. So our experience was defined patient after patient, result after result, data after data.

### 1.2. First Case

The history of our experience in the application of Cytosorb in the pediatric field starts from May 2016 up to nowadays and was written "*patient after patient*" along a horizon of different applications: a success based on the collaboration between different specialists.

The use of CytoSorb allowed us to obtain a rapid improvement of the hemodynamic conditions, the upgrading of renal and pulmonary functions, the reduction of vasopressors and the resolute reduction of "*cytokine storm*" in several dramatic condition [1-2].

We observed a marked decrease in inflammatory mediators, a reduction in catecholamine dosages and an improvement in organ functions, which was particularly pronounced in patients who survived. An early onset of treatment (at best within 24-48 hours after diagnosis of sepsis) seemed to be beneficial for eventual survival [1]. These results were not "*our first aim or intention*" when we applied Cytosorb for the

first time. Everything started by chance in a critical moment: in May 2016 a six years patient, 21 kg weight, was having in extracorporeal assistance a pediatric cardiac surgery procedure, a "*Fontan treatment at its third surgical Redou*".

The patient was having an intractable surgical and medical bleeding due to surgical procedural difficulties and requirement of massive administration of blood, FFP, platelets, coagulation factors. The more the patient was bleeding the more the surgeon could not make correct sutures the more we administered volume but the patient was dying for bleeding. We decided to apply a Cytosorb filter on the field blood recovery machine in post reservoir bag position and started to give to patient Cytosorb filtered blood. In a few minutes the bleeding became normal and the procedure was completed. We noted how the postoperative bleeding was very trivial. Some order of problems came to our attention: first we had used a device not released for pediatric patients weighting less than 40 kg without parents permission; second there was no ethical committee authorization and this situation convinced us that we could not repurpose the use of Cytosorb. Last but not least, in the aim to have more data a very accurate bibliographic research about the use of Cytosorb in pediatric field was done but no article was found. We found in literature that the use of Cytosorb in adults surgical bleeding leads:

1. Limits and does not amplify the Coagulation Cascade and the activation of the Complement (Cfr. Figure 1-Patient Case Number 9)
2. Limits elimination and consumption of Fibrinogen: 340 KD
3. Limits the elimination and consumption of coagulation factors; AT III
4. Is not relevant in elimination of Albumin
5. Has poor impact on platelets

A clinical sperimental research work was proposed to the Ethical Committee of our institution, but a long time passed without a response. In the meanwhile the Ethical committee authorized us in the use of Cytosorb in patients "*imminentia mortis*"

Case	Age (months)	Gender	Weight (kg)	BMI	Diagnosis	Microbiological findings
1	1	M	3.5	14	RVAPT	Candida parapsilosis
2	82	F	16	13.2	ARDS, Sepsis	Pseudomonas aeruginosa, Candida albicans, Klebsiella pneumoniae, Torulopsis glabrata
3	48	F	19	19	HLH, Sepsis	Clostridium difficile, Streptococcus pneumoniae
4	126	F	35	17.8	Acute myocarditis	Streptococcus pneumoniae
5	17	F	10	13.8	HUS, septic shock	Escherichia coli O157
6	312	F	52	21.6	Acute myeloid leukemia, sepsis	Clostridium difficile, Candida krusei, HHV6
7	60	M	25	21	ADEM	HHV7, Acinetobacter baumannii, Haemoliticus spec.
8	11	M	10.6	21.6	Septic arthritis, sepsis	β-hemolytic streptococcus, Staph aureus
9	6	F	8	22	Fontan procedure complicated by severe bleeding and prolonged cardiopulmonary bypass	none (Cytosorb used during prolonged extracorporeal circulation)
10	9	F	4.8	17.5	CAVC, sepsis	Proteus mirabilis, Candida parapsilosis, Metapneumovirus

Case	No of organs failures	No of CytoSorb treatments	CytoSorb treatment durations	Delay CytoSorb therapy start (hours after diagnosis of sepsis)	Specific CytoSorb priming procedure Y/N	Mechanical ventilation (days)
1	Hem, Ren, Res, Hep, Coa, Neu	1	19 hours	>48 hours	Y	38
2	Hem, Ren, Res	3	54 hours (19 h per treatment)	24-48 hours	Y	22
3	Hem, Ren, Res, Coa	3	60 hours (20 h per treatment)	<24 hours	Y	4
4	Hem, Ren, Res, Neu	2	48 h (24 h per treatment)	>48 hours	Y	6
5	Hem, Ren, Res, Coa, Neu	2	36 h (18 h per treatment)	>48 hours	Y	4
6	Hem, Ren, Res, Hep, Neu	2	38 hours (19 h per treatment)	>48 hours	Y	8
7	Hem, Ren, Res, Neu	3	57 hours (19 h per treatment)	24-48 hours	Y	29
8	Hem, Ren, Res, Coa	2	48 hours (24 h per treatment)	<24 hours	Y	5
9	Hem, Ren, Res, Coa	1	6 hours	<24 hours	Y	4
10	Hem, Ren, Res, Coa, Hep	3	52 hours (17 h per treatment)	24-48 hours	Y	21

Case	Catecholamines (days)	ECMO (days)	CRRT (days)	ICU LOS (d)	ICU survival (y/n)	Comment
1	38	20	20	38	NO	The patient died after 38 days on ICU from cardiac failure
2	5	0	2	17	YES	Survival and discharged from hospital
3	8	0	5	14	YES	Survival and discharged from hospital
4	6	6	6	6	NO	The patient died after 6 days on ICU from encephalitis and cerebral death
5	4	2	8	4	NO	The patient died after 4 days on ICU from irreversible cardiac failure
6	7	0	2	7	NO	The patient died after 7 days on ICU from septic shock (Cytosorb applied too late > 48h)
7	12	0	3	23	YES	Survival and discharged from hospital
8	2	0	3	6	YES	Survival and discharged from hospital
9	4	1	0	7	YES	Survival and discharged from hospital
10	10	16	7	30	NO	The patient died after 30 days on ICU (due to non septic reasons, i.e. massive aortic valve insufficiency)

Res: respiratory

Hem: Hemodynamic

Ren: renal

Hep: hepatic

Coa: Coagulation

Neu: Neurologic

RVAPT: Total anomalous venous pulmonary return

HLH: Hemophagocytic lymphohistiocytosis

HUS: Hemolytic uremic syndrome

ADEM: Acute disseminated encephalomyelitis

CAVC: Complete atrioventricular canal defect

**Figure 1.** Our First Ten Patient characteristics, treatment modalities and patient outcome.

(Published on Leonardo Milella, Maria Teresa Ficarella, Gerolmina Calabrese, Michele Sisto, Rita Luana Grieco, Paola Moliterni, Pasquale Raimondo, Fabiana Cito, Vito Bellino, Antonio Ranieri, Mario Giordano. Application of Hemoadsorption in Neonatal and Pediatric Hyperinflammatory States: A Case Series. American Journal of Pediatrics. Vol. 5, No. 2, 2019, pp. 34-42. doi: 10.11648/j.ajp.20190502.1.

### 1.3. Second Case: The Treatment of a Secondary Hemophagocytic Lymphohistiocytosis Using Cytosorb

We did not use Cytosorb until July 2016 when a 4-year-old patient is hospitalized in severe clinical conditions in our ICU. The patient had been recovered in our institution since 25 days for fever and hyposthenia, increased of white blood cells count (WBC), Presepsine levels, (PRS) and Procalcitonine levels (PCT). During this period the patient received many laboratoristic tests, cultural spread tests, imaging test at different anatomical districts CT Scan; Magnetic Resonance Scan (MRI), Ecographic with no evidence of infection or metabolic or neurological pathology. In the last three days was decided to perform a video laparoscopic procedure for appendicitis but the patient was abdominal disease free. For the worsening of clinical conditions, the patient came to our ICU.

She had:

1. Sensor in rapid deterioration
2. Fever (39°C degrees)
3. Unstable hemodynamics (FC 150 bpm; MAP <50 mmHg)
4. Worsening of Respiratory Exchanges and subsequent Intubation
5. Anuria
6. Altered Laboratory Exams: 35 WBC, PCR and PCT are rapidly increasing
7. Myoglobin value rapidly increasing
8. Bilirubin total value rapidly increasing
9. PRS and PCT rapidly increasing
10. Ascites
11. Evidence of DIC

We started a septic shock and sepsis treatment with CRRT

and Plasmapheresis. Vasoconstrictive drugs, fluid infusion and antibiotics but there was an hitherto non responder clinical condition. We decided to apply a Cytosorb treatment declaring the “Imminentia Mortis” of the patient and the Cytosorb as rescue treatment to parents having the approval to the procedure, (Tables 1-2).

**Table 1.** Priming was done with blood.

Techniques	Priming/mls	Flow mls/min	Duration-Days
CVVHDF	58	150-350	5
Plasmapheresys	67	1500-2000 mls/h	5
Cytosorb	180	90	3

**Table 2.** Treatment

CVVHDF	5 TREATMENTS
PLASMAPHERESYS	5 TREATMENTS
CYTOSORB	3 TREATMENTS

Published on Milella L and Ficarella MT. First application of CVVHDF, plasmapheresis and “Cytosorb Absorber” to solve a pediatric Haemophagocytic Histiocytosis case. Crimson publisher. December 8, 2017.

This is a Case Report of Secondary hemofagocytic lymphohistiocytosis as a consequence of infection (Streptococcus Pneumoniae) with a contextual transitory deficit of perforine

protein that developed an acute syndrome with macrophage activation, septic shock and sepsis. There was a clear evidence of the usefulness of Cytosorb action in the healing of the patient, (Figure 1 - Case 3). This was a turning point case for many reasons: gave us the chance to start an off-label use of Cytosorb even in patients weighting less than 40 kg. This situation permitted us to submit a structured and clinical reliable protocol of Cytosorb application at the analysis of Ethical Committee that gave us, in the hitherto of taking a decision, the permission to use Cytosorb in “Imminentia Mortis” cases. This condition convinced us that the operating modality and scientific principia of Cytosorb where different from other CRRT techniques especially for the rapidity of its action; convinced us that a device structured and released for adults treatment could be used even in pediatrics with many attentions and property of skills by operators. In the meanwhile we continue to use Cytosorb in every “Imminentia Mortis” clinical condition do to septic shock, sepsis, MOF.

#### 1.4. Dedicated Lab Test Protocol

The first step was to structure and define a lab tests protocol that could give us a very rapid and short control over Cytokines levels during Cytosorb use, (Table 3).

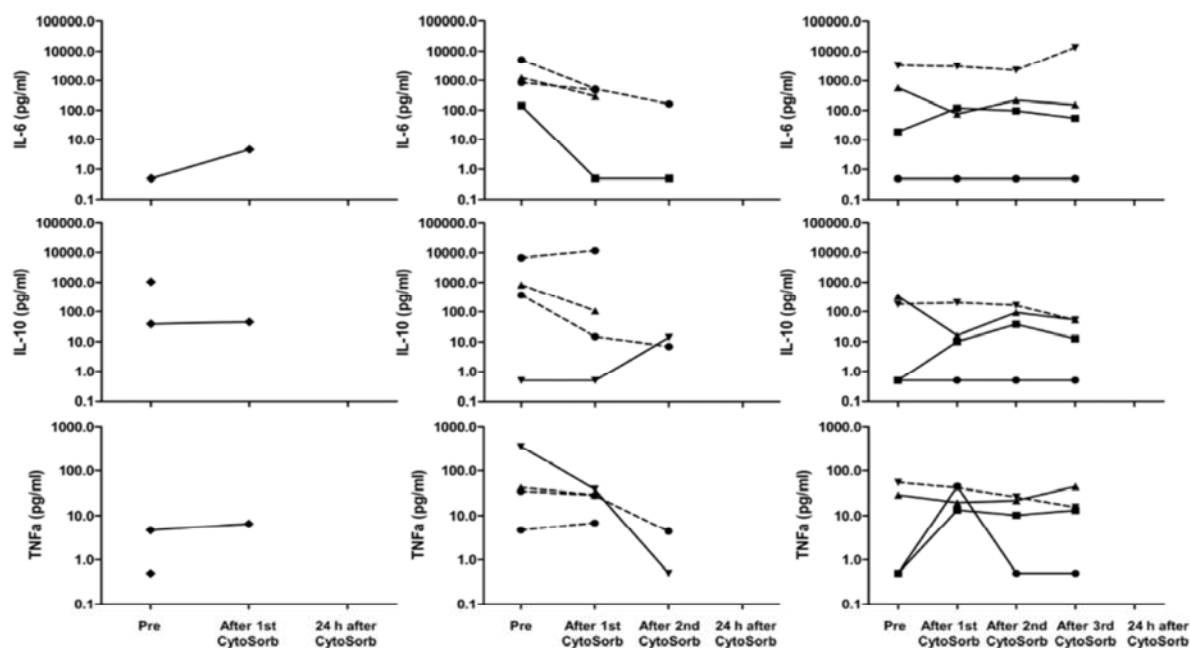
**Table 3.** “Specific Cytosorb Lab Tests”.

ZERO TIME BEFORE CYTOSORB APPLICATION
Patient anamnestic data; weight; height, body surface; clinical step of Cytosorb application
Hemoglobine
Myoglobine
Free Hemoglobine
TNFα, IL-6, IL-10; 5 ml of serum centrifugate and stored at -80 degree
8 HOURS AFTER CYTOSORB APPLICATION AND EVERY 8 HOURS DURING PROCEDURE
Hemoglobine
Myoglobine
Free Hemoglobine
TNFα, IL-6, IL-10; 5 ml of serum centrifugate and stored at -80 degree
AT SUSPENSION OF CYTOSORB APPLICATION
Hemoglobine
Myoglobine
Free Hemoglobine
TNFα, IL-6, IL-10; 5 ml of serum centrifugate and stored at -80 degree
AT 24 HRS AFTER SUSPENSION OF CYTOSORB APPLICATION
Hemoglobine
Myoglobine
Free Hemoglobine
TNFα, IL-6, IL-10; 5 ml of serum centrifugate and stored at -80 degree

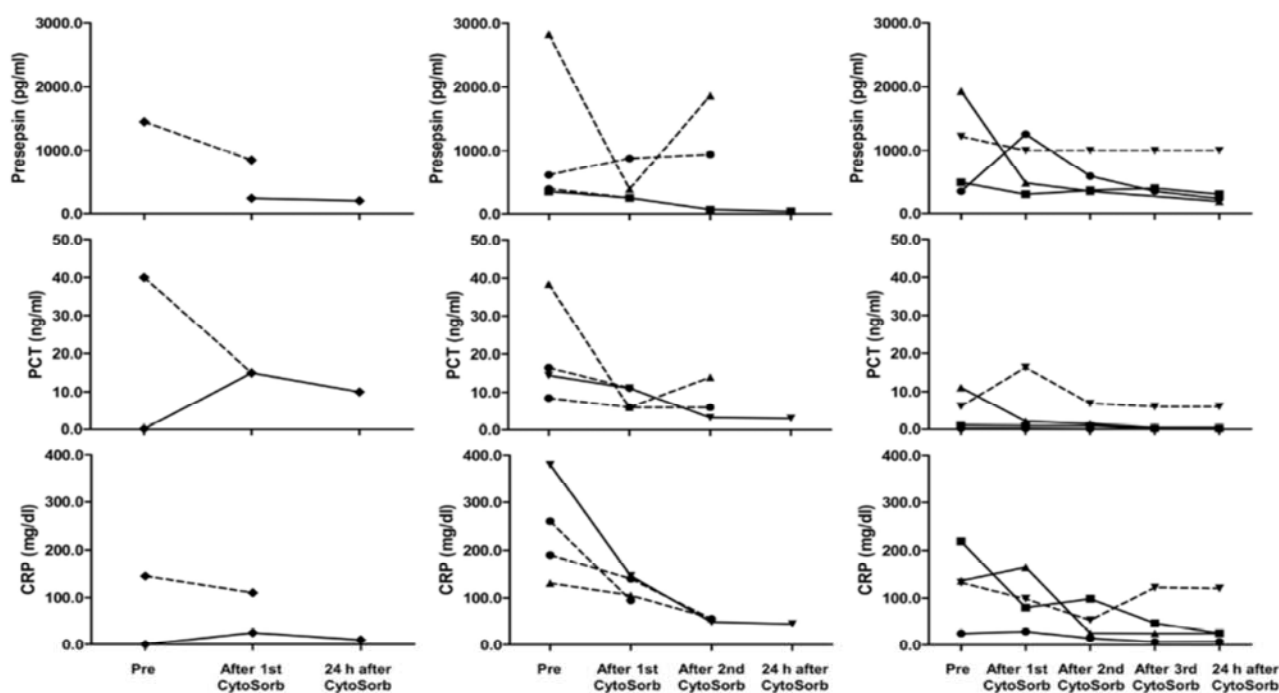
#### 1.5. Specific Lab Test Result

The second step was to collect a reasonable number of samples; the last step was to ask Fresenius Clinical Medical GmbH – Berlin, Germany to do all the tests regarding the Cytokine levels (Figures 2 - 3 - 4). From left to right images for each parameter display patients receiving 1 (left), 2 (middle) or

3 (right) Cytosorb treatments, respectively. Values were assessed directly prior to treatment (pre), immediately after termination of each treatment (after Cytosorb) and 24 hours after termination of the last treatment (24 hours after Cytosorb). Solid lines indicate ICU survivors, dashed lines represent ICU non-survivors. Please note that some data were not available from all patients.



**Figure 2.** Levels of IL-6, IL-10, and TNF $\alpha$  during the course of treatment. From left to right images for each parameter display patients receiving 1 (left), 2 (middle) or 3 (right) CytoSorb treatments, respectively. Values were assessed directly prior to treatment (pre), immediately after termination of each treatment (after CytoSorb) and 24 hours after termination of the last treatment (24 hours after CytoSorb). Solid lines indicate ICU survivors, dashed lines represent ICU non-survivors. Please note that some data were not available from all patients.



**Figure 1.** Levels of presepsin, PCT and CRP during the course of treatment. From left to right images for each parameter display patients receiving 1 (left), 2 (middle) or 3 (right) CytoSorb treatments, respectively. Values were assessed directly prior to treatment (pre), immediately after termination of each treatment (after CytoSorb) and 24 hours after termination of the last treatment (24 hours after CytoSorb). Solid lines indicate ICU survivors, dashed lines represent ICU non-survivors. Please note that some data were not available from all patients.

**Figure 2.** "Specific CytoSorb Lab Tests results".

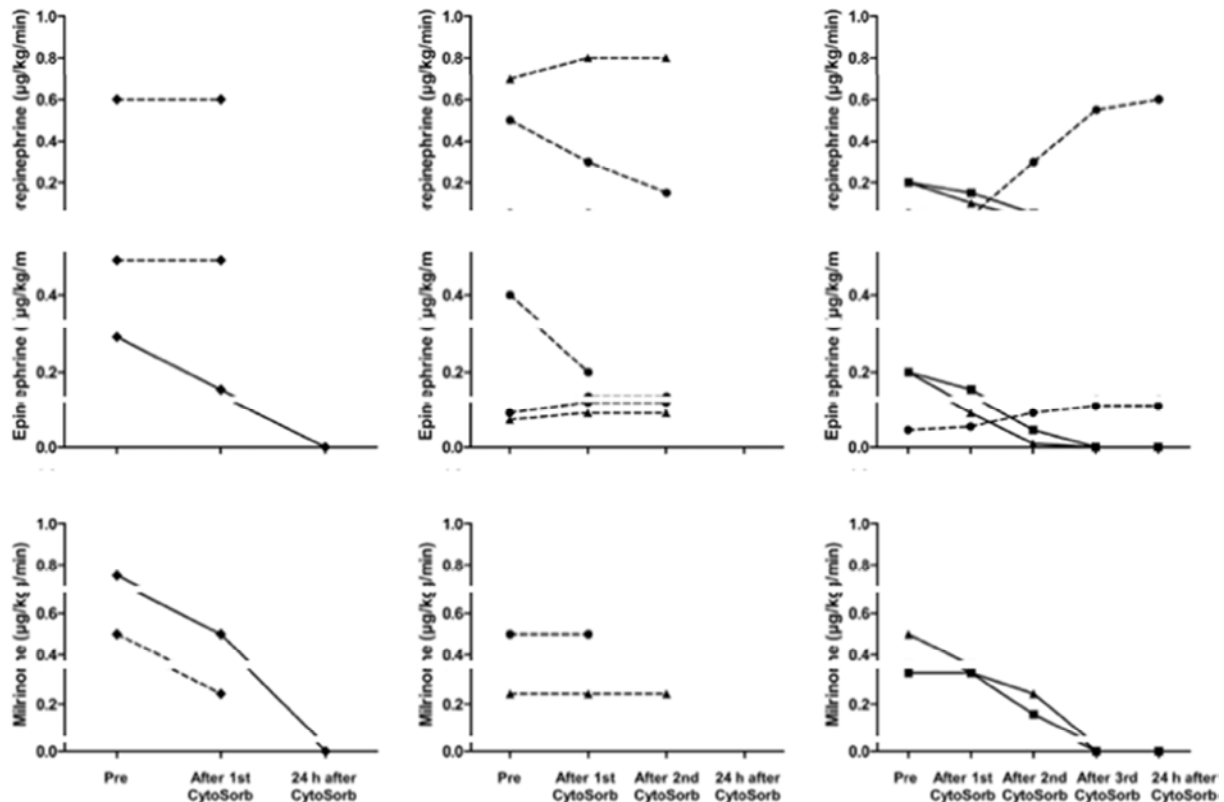


Figure 3. Development of catecholamine need during the course of treatment.

(Published on Leonardo Milella, Maria Teresa Ficarella, Gerolmina Calabrese, Michele Sisto, Rita Luana Grieco, Paola Moliterni, Pasquale Raimondo, Fabiana Cito, Vito Bellino, Antonio Ranieri, Mario Giordano. Application of Hemoabsorption in Neonatal and Pediatric Hyperinflammatory States: A Case Series. American Journal of Pediatrics. Vol. 5, No. 2, 2019, pp. 34-42. doi: 10.11648/j.ajp.20190502.11).

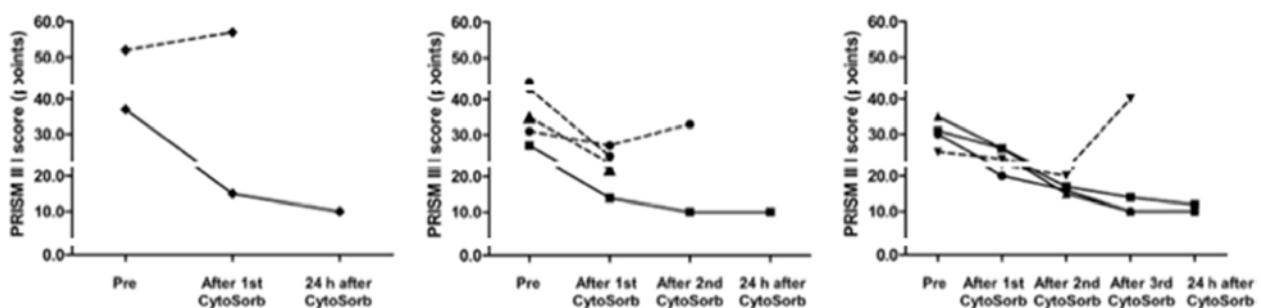


Figure 4. PRISM III scores during the course of treatment.

(Published on Leonardo Milella, Maria Teresa Ficarella, Gerolmina Calabrese, Michele Sisto, Rita Luana Grieco, Paola Moliterni, Pasquale Raimondo, Fabiana Cito, Vito Bellino, Antonio Ranieri, Mario Giordano. Application of Hemoabsorption in Neonatal and Pediatric Hyperinflammatory States: A Case Series. American Journal of Pediatrics. Vol. 5, No. 2, 2019, pp. 34-42. doi: 10.11648/j.ajp.20190502.11).

#### 1.6. MOF During Neonatal and Pediatric ECMO or Cardiopulmonary By-pass for Cardiac Surgery

A new horizon of application came to us when we decided to try to overtake the huge amount on difficulties that Cytosorb application could present in very dramatic conditions: Terminal MOF during neonatal and pediatric extracorporeal mechanical support (ECMO) or neonatal Cardiopulmonary by-pass for cardiac surgery.

There were procedures done again during “Imminencia mortis”, but data showed us that Cytosorb use could be applied even in neonates in very dramatic clinical conditions

with good results;

The application technique was relatively changed because of the assisted flow but, during the procedure, we had to change the site of Cytosorb position because the increase of flow and priming was having an important effect on the ECMO or CPB flow.

There also was interference from the ventilator assistance due to the changes in toracopolmonary interaction causing alteration of pulmonary V/Q distribution; all these interferences did not permit to reach a good peripheral perfusion.



**Figure 5.** Neonatal ECMO support with CRRT and Cytosorb.



**Figure 6.** Neonatal Cardiopulmonary By Pass with CRRT and ECMO.

We decided to not staple the CRRT and Cytosorb circuit in a sequential mode on the ECMO or CPB circuit but to cannulate the patient in different sites and treat the blood directly from the patient and not the pump blood (Figures 5-6). The pump flow was increased of 20%.

We also decided to give rescue ventilation to patient using the less PEEP and the most respiratory ventilation frequency able to set up the mean airway pressure in a plateau stable interval within 13 and 15 CmH<sub>2</sub>O.

We gave the patient a basal dosage of catecholamines even during assistance. If we consider data showed in our article from June 2019 it is very comfortable to see how valuable was the technique.

We observed:

1. *A very rapid recovery of clinical conditions*
2. *Rapid slope of hypnotropic drugs*
3. *Rapid recovery of hepatic failure*
4. *Rapid recovery of renal failure*
5. *Rapid recovery of lung disease*
6. *Rapid improvement of inflammation levels (cytokines drop down) (figures 2-3-4)*

Data in figures 2-3 show that Cytosorb also in this particular application was very useful in treating the MOF but even show that two neonatal patients died: the first for cerebral death and the second for huge aortic valve dysfunction.

In our opinion this does not represent a limit in Cytosorb neonatal use: according with recent literature these two events happened after 28 days from the end of the use of Cytosorb and did not affect the principles and the scientific and clinical use of Cytosorb.

Another step in our pathway came in the mild 2018; it gives us the chance to think about some valuation, error that

permitted us to start a different Cytosorb application protocol and new ideas.

### 1.7. The Treatment of Acute Hemorrhagic Encephalitis

A 5-year-old boy (weight 29 kg) was admitted to a peripheral hospital after he had a syncopal episode at school along with a short (few days) history of vomiting and difficulties in walking, (Figure 1- Case 8). Upon direct admission to the ICU, the patient presented with significant hyposthenia in his limbs, dysmetria, nystagmus and uncoordinated pupillary movement.

Cerebral CT scan showed areas of diffuse bilateral hypodensity in the supra and subtentorial areas with lesions most probably of an infectious-inflammatory nature.

The neurosurgeons excluded the need to intervene surgically considering the likelihood of infectious lesions, therapy with inotropic and vasodilative drugs, diuretics, corticosteroids, immunoglobulins, IgG, and antibiotics (ceftriaxone) were started immediately, blood red cells and fresh frozen plasma were also given and a continuous infusion of albumin 20% was started as for protocol at 2 ml/hr.

Examination of bronchial sample was positive for *Acinetobacter Haemolyticus*, while direct virological testing from pharyngeal swabs was positive for Human Herpes Virus 7 (HHV-7).

So, a Plasmapheretic treatment in albumin was started, as CRRT in CVVHD at a flow of 300 ml/h.

About anticoagulation: we used a low molecular weight sodium heparin at a rate of 5 IU/kg/h. Therapy resulted in removal of inflammatory mediators, improvement in the hemodynamic, neurological and overall clinical condition, ventilatory insufficiency was treated with extubation in two days, MOF dysfunction lab test reduces; in a six days time it was decided to dismiss the patient.

In two days time the patient represented the overall symptoms and came in ICU in very critical condition.

To support the pharmacological treatment of coma, sepsis, and MOF a first step Cytosorb treatment was applied:

1. 3 treatments with Cytosorb for a total treatment time of 54 hours (18 hours each treatment) separated by pause intervals of 6 hours
2. Cytosorb was used in conjunction only with CRRT (Prismaflex, Gambro) run in CVVHDF mode
3. No plasmapheretic treatment was done
4. Blood flow: 90 ml/min
5. Dialysis flow: 300 ml/h
6. Anticoagulation: low molecular weight sodium heparin at a rate of 5 IU/kg/h
7. Cytosorb position: post-hemofilter; red blood cell priming of 90 ml was used

The case of this patient with acute hemorrhagic encephalitis, cerebral edema and multiple organ failure and the clinical therapeutically events suggested us that in order to treat these MOF from different etiologies our idea tending to start with Cytosorb use as first treatment or rescue treatment had to be considered;

The combined treatment with CRRT and Cytosorb followed

by plasmapheresis could be the goal of therapy resulting in the rapid removal of inflammatory mediators, and an improvement in the hemodynamic, neurological and overall clinical condition.

As the resolution of coma, respiratory insufficiency, renal and metabolic failure occurred shortly after the first discharge of patient, Cytosorb treatment should probably have already been initiated during the first recovery instead of apheresis, not waiting for a subsequent evidence of not correct and exhaustive disease therapy.

This evidence was confirmed from the analysis of cytokines level data, and from the analysis of clinical data showed in figures 2-3-4:

1. *It was clear that Cytosorb has to be applied as first choice;*
2. *Application timing had to be not more than 18 hours due to absorption default;*

Important: In all the not survived patients there has been a persistent high IL10 level.

This last parameters was very impressive: IL-10 is known to be an important index of the organic response to aggressive pathogens and its high levels always led us to think that there was an adequate immunity response.

We made some considerations: the mainly problem of Cytokine storms is the velocity of release of pathologic mediators, it is very difficult to stop these release in very short time and break the chains of an auto-sustaining mediators release.

When you use an apheretic filter a quote of mediators is not removed and goes further circulation sustaining the immunity deficitary response. The best therapeutic result cannot avoid the removal of circulating mediators: Cytosorb use aloud us to do it.

Consequently a persistent or increasing high level of IL-10 indicates a negative prognostic sign, as we published in "Use of Cytosorb in a pediatric case of acute hemorrhagic encephalitis and multiple" organ failure, Case of the Week in Cytosorb Literature Database, (L. Milella 14/2018).

### 1.8. The Treatment a Case of Septic Shock Due to Streptococcal Arthritis

We were strongly convinced of our ideas in March 2019 when we treated a case of septic shock due to Streptococcal Arthritis (Figure 1 - Case 8). A 4 years old patient weighing 16 kg was admitted to our unit from Orthopedic Unit where he was treated for Streptococcal Arthritis. At the admission of the patient he was in very critical condition due to coma, respiratory insufficiency, septic shock and MOF, cardiogenic shock (table 4).

**Table 4.** Patient Data at the admission in ICU.

Hypotension	MAP< 40 mmHg
Tachycardia	175 bpm
Fever	38,8°C
GCS	7
pH	7.19
PaO2	75 mmHg
PaCO2	55 mmHg
Lactate	5.5 mmol/L
Be	-12 mmol/L
PRC	480 mg/dL
PLT	50000

Our protocol for treatment of Septic Shock, Sepsis, MOD was started as previously referred. CRRT was immediately started as CVVHD and an emoadsorbent cartridge (Cytosorb) was integrated in a post-hemofilter position in the traditional CRRT circuit. Continuous veno-venous hemodiafiltration (CVVHDF) flow ranged from 20-30 ml/kg/h, ultrafiltration rate was variable with hemodynamics; heparin anticoagulation (5-30 IU/Kg/h) was controlled with activated clotting time (ACT: 150-200 sec), APTT-INR (1.5-1.8), Thromboelastogram (TEG), every 4 hours. The first treatment had a duration of 18 hours separated from the second one by a 24 hours pause interval, to verify improvements in PRISM III and SOFA score; Clinical and biochemical parameters were measured daily. There was a sudden improvement of patient clinical conditions (Table 5):

**Table 5.** Patient Data before, during and after the treatment.

DATA	Before 1 <sup>st</sup> Treatment	After 1 <sup>st</sup> Treatment	After 24 hours
Norepinephrine	0.05 µg/kg/min	0.03 µg/kg/min	0
IL-6	140 pg/ml	0.5 pg/ml	0.5 pg/ml
TNFα	351 pg/ml	38 pg/ml	0.5 pg/ml
SOFA Score	27	10	
PRISM III Score	18	9	

(P. Raimondo, M. Ficarella, P. Moliterni, M. Sisto, F. Cito, G. Calabrese, L. Milella Pediatric Department of Neonatal and Pediatric Anesthesia and Intensive Care Unit – Neonatal and Pediatric Cardiac Anesthesia and ICU; Giovanni XXIII Hospital – Policlinico di Bari (Italy); Blood Purif 2019; 47 (suppl 4): 3–37 31DOI: 10.1159/000500179).

The patient was extubated in 3<sup>d</sup> day and dismissed in 6<sup>th</sup> day. It is our conviction that the immediate use of Cytosorb allowed us to obtain a rapid improvement of the hemodynamic conditions, of renal and pulmonary functions, reduction of vasopressors and resolute reduction of "cytokines storm", a not rare deadly event even in pediatric patients, (we broke the auto - sustaining chain), as we published in Single Pediatric Case Recovery for Septic Shock Due to Streptococcal

Arthritis Using Early Extracorporeal Cytokine Adsorber Treatment, (P. Raimondo, M. Ficarella, P. Moliterni, M. Sisto, F. Cito, G. Calabrese, L. Milella Pediatric Department of Neonatal and Pediatric Anesthesia and Intensive Care Unit – Neonatal and Pediatric Cardiac Anesthesia and ICU; Giovanni XXIII Hospital – Policlinico di Bari (Italy); Blood Purif 2019; 47 (suppl 4): 3–37 31DOI: 10.1159/000500179).

## 2. Albumin and Sepsis

According with Archimedes' thought: "give me a lever and a foothold and I will rise up the world", it is our strong opinion since a long time that if we look at Blood as a body well defined System with a single organ philosophic working attitude, very complex indeed, but very multicovariate defined, Albumin is our "lever" and "blood reology" is our foothold.

In our unit we where use to treat since 2005 every patient recovered because affected from viral infections with plasmapheresis.

Until six years ago we performed only plasma exchange apheresis, but, according with our thoughts, we ipotized that body wather overload was the first problem in SIRS or septic patients and peripheral cellular leakage, as well, was either due to oligoanuria or fluid overload was at the basis of clinical conditions of the patient and worsening of mortality and morbidity.

This opinion led us to not overload the patient with large fluid intake (or cristaloids, or plasma expanders) but to apply CRRT (CVVHF) as a routinary treatment to avoid fluid overload and peripheral leakage.

We change our first step infectious desease treatment and we stared to give at every patient, independently from weight and age, a 2 ml/hour albumin 20% infusion to take Albumin levels not less than minimal range value, (20-48 mg/dl).

We were convinced that among the multiple albumin functions, to administer albumin in continuous infusion to avoid lost of it or to correct low levels was the first and better choice for the patient in the aim to administer noble fluid replacement, increase the plasmatic osmolarity and to recall water and liquids from third space into plasma.

The second step was to perform albumin driven plasmapheresis and support immunity response with fresh frozen plasma administration at not less than 20 ml/kg/ day.

Albumin functions are more than to maintain plasmatic reology (Figure 7); a default in albumin level could be done from less intake, reduced concentration caused by fluid overload, more oxidation, post transcriptional changes in isoforms. Many studies have been done in the last decade confirming the role of albumin in many pathological situations, (Figure 7).

This is because it is accleared that Albumin is the most abundant plasma source of anti-oxidant agents in the extra-cellular space due to the free Cys-34.

Cys-34 is a thiole acid component and represents the level of oxidate cysteine in human serum albumin level (HA) Low Cys-34 levels have a deep impact in the ligand albumin-nitric oxide giving to this ligand a stabilizations. In a few words Cys-34 stabilizes the link and carrying on nitric oxide to albumin and its distribution to BioPhase and cellular receptors during sepsis contributing to decrease the peripheral vascular microembolization [31]. It is ineludible that severe sepsis is associated with a large increase in albumin oxidation:

There are two type of albumin oxidative pathways:

The first one is the so called HNA-1 that is a reversible oxidative action, and the second one i NHA-2 that is irreversible oxidative reaction.

Both these oxidative reactions lead to a decrease in the level of metalbumin levels (HMA) the active form of circulating albumin.

This not reversible process (HNA-2) of albumin oxidation may be associated with an increased mortality and morbidity during sepsis, whereas a reduced average serum albumin may oppose the solution of primary infection. [32]

The Italian Multicenter Study "Albios" 33 confirmed the central role of albumin levels in sepsis and infectious disease pathologies. [33]

In the end we are sure that albumin normal level is on of the principal driven of sepsis treatment.

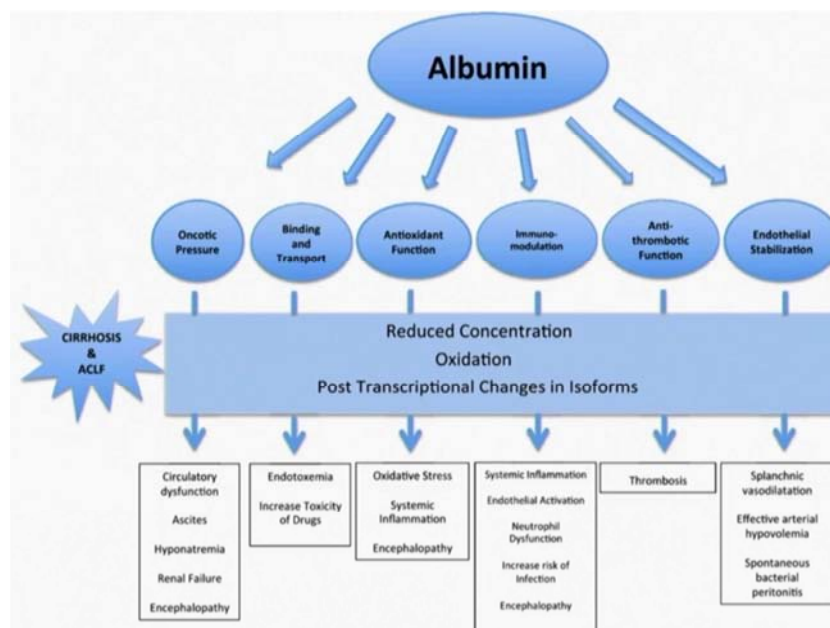


Figure 7. Albumin.

### 3. Other Horizons: Hemolytic Huremic Syndrome and Bridge for Liver Transplantation

We already used Cytosorb treatment in 20 MOF sepsis related patients with last 5 patients survived at treatment, this data are on the way to be published.

It is compulsory to us to point out that we enlarged the use of Cytosorb in patients not strictly affected from MOF sepsis related but also affected from peculiar pathologies potentially deadly.

Two experienced examples can be helpful:

The use of Cytosorb could represent a new adjuvant therapeutic approach in the treatment of septic shock–HUS related, its efficacy leads less vasoplegia, better hemodynamic, reduction of vasopressor drugs. A difference of the only case in the literature, we use a triple therapy: CVVHDF, early use of Cytosorb; PEX. In a four years patient that survived without neurological sequel.

In pediatric patients, acute liver failure caused by different insults to the liver, represents a critical condition and requires timely intervention with liver transplantation for the survival. In a case of a six-month-old patient, agonic with coagulation dramatic alterations and MOF we use Cytosorb rescue treatment of 18 hours before leading it to liver transplant the patient survived.

Using Cytosorb as a bridge to transplant in a case of severe Hepatic Failure can reduce morbidity and mortality and obtain a better to long-term survival in pediatric patient.

### 4. Conclusions

This was the report of our unit journey during almost four years time in the treatment of sepsis and sepsis related MOF.

And this will be not a conclusion strictly correlated to our results during this journey.

This will be a personal consideration about a change in our way to approach the patient treatment.

But also we tried to show how many changes have been done in application of therapies during this period according with our new approach.

Starting from the basis of previous experience and new therapeutical ideas, we changed our way to look after the patient only in a very schematic and guidelines-protocols guided asset.

Cytosorb was extremely useful in giving the patient a new way of treatment in sepsis, SIRS and many clinical conditions that coul'd lead to patient death.

But the principal change in our therapeutic treatment was to consider Blood as an organ, a system with a proper philosophy of work and probably the center of our anatomical and physiological structure.

This speculation convinced us that the way to propose for sepsis or MOF treatment is not unitary but requires a global vision of the patient response to it, especially from one point

of view: our aim has to be accompany nature, to go with the nature, to bring back every single organ to its work philosophy.

This opinion seems to be very difficult to express and much more to be understood because we need results, we need patient survive and therapy is our sword to fight against aggressive pathogens or genetical conditions or immunity deficiency, but we can't forget what Dr William Osler communicated us in the early 1900 years: "Except in few occasions, the patients seems to die from the body's response to infection rather than from it".

Further studies are needed from several points of view and not least may be that a new consideration about human behavior and nature philosophy relationship has to be studied

### Statement of Ethics

None of the Authors has a personal interest and the research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

### Disclosure Statement

The authors have no conflicts of interest to declare.

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### Authors' Contributions

All the Authors.

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### References

- [1] Leonardo Milella, Maria Teresa Ficarella, Gerolmina Calabrese, Michele Sisto, Rita Luana Grieco, Paola Moliterni, Pasquale Raimondo, Fabiana Cito, Vito Bellino, Antonio Ranieri, Mario Giordano. Application of Hemoadsorption in Neonatal and Pediatric Hyperinflammatory States: A Case Series. *American Journal of Pediatrics*. Vol. 5, No. 2, 2019, pp. 34-42. doi: 10.11648/j.ajp.20190502.11.
- [2] Milella L and Ficarella MT. *First application of CVVHDF, plasmapheresis and "Cytosorb A Bsorber" to solve a pediatric Haemophagocytic Histiocytosis case*. Crimson publisher. December 8, 2017.
- [3] P. Raimondo; MT. Ficarella; P. Moliterni; M. Sisto; F. Cito; G. Calabrese; L. Milella. *Use of Cytosorb in a Pediatric patient with septic shock due to streptococcal arthritis*. Case of the week. 18/06/2019.
- [4] Rimmele T, Kellum JA: Clinical review: blood purification for sepsis. *Crit Care* 2011; 15: 205.

- [5] Trager K, Fritzler D, Fischer G, et al: Treatment of postcardiopulmonary bypass SIRS by hemoadsorption: a case series. *Int J Artif Organs* 2016; 39: 141-6.
- [6] Datzmann T, Trager K: Extracorporeal membrane oxygenation and cytokine adsorption. *J Thorac Dis* 2018; 10: S653-S660.
- [7] Honore PM, Jacobs R, Joannes-Boyau O, et al: Newly designed CRRT membranes for sepsis and SIRS-- a pragmatic approach for bedside intensivists summarizing the more recent advances: a systematic structured review. *ASAIO J* 2013; 59: 99-106.
- [8] Eyre M, Hachohen Y, Barton C, et al: Therapeutic plasma exchange in paediatric neurology: a critical review and proposed treatment algorithm. *Dev Med Child Neurol* 2018; 60: 765-779.
- [9] Milella L: Neonatal and Pediatric General and Cardiac Anaesthesia and ICU: with a new in 2017/2018? -Bari Pediatric Hospital Experience-Italy." *Journal of Pediatrics and Neonatal Care* 2018; 8: 00309.
- [10] Bonavia A, Groff A, Karamchandani K, et al: Clinical Utility of Extracorporeal Cytokine Hemoadsorption Therapy: A Literature Review. *Blood Purif* 2018; 46: 337-349.
- [11] Song M, Winchester J, Albright RL, et al: Cytokine removal with a novel adsorbent polymer. *Blood Purif* 2004; 22: 428-34.
- [12] Gruda MC, Rugeberg KG, O'Sullivan P, et al: Broad adsorption of sepsis-related PAMP and DAMP molecules, mycotoxins, and cytokines from whole blood using CytoSorb® sorbent porous polymer beads. *PLoS One* 2018; 13: e0191676. *American Journal of Pediatrics* 2019; 5 (2): 34-42.
- [13] Hotchkiss RS, Karl IE: The pathophysiology and treatment of sepsis. *N Engl J Med* 2003; 348: 138-50.
- [14] Spittler A, Razenberger M, Kupper H, et al: Relationship between interleukin-6 plasma concentration in patients with sepsis, monocyte phenotype, monocyte phagocytic properties, and cytokine production. *Clin Infect Dis* 2000; 31: 1338-42.
- [15] Kellum JA, Kong L, Fink MP, et al: Understanding the inflammatory cytokine response in pneumonia and sepsis: results of the Genetic and Inflammatory Markers of Sepsis (GenIMS) Study. *Arch Intern Med* 2007; 167: 1655-63.
- [16] Kellum JA, Song M, Venkataraman R: Hemoadsorption removes tumor necrosis factor, interleukin-6, and interleukin-10, reduces nuclear factor-kappaB DNA binding, and improves short-term survival in lethal endotoxemia. *Crit Care Med* 2004; 32: 801-5.
- [17] Hetz H, Berger R, Recknagel P et al: Septic shock secondary to  $\beta$ -hemolytic streptococcus-induced necrotizing fasciitis treated with a novel cytokine adsorption therapy. *Int J Artif Organs* 2014; 37: 422-6.
- [18] Bruenger F, Kizner L, Weile J, et al: First successful combination of ECMO with cytokine removal therapy in cardiogenic septic shock: a case report. *Int J Artif Organs* 2015; 38: 113-6.
- [19] Pinsky MR, Vincent JL, Deviere J, et al: Serum cytokine levels in human septic shock. Relation to multiple-system organ failure and mortality. *Chest* 1993; 103: 565-75.
- [20] Saraiva M, O'Garra A: The regulation of IL-10 production by immune cells. *Nat Rev Immunol* 2010; 10: 170-81.
- [21] Friesecke S, Stecher SS, Gross S, et al: Extracorporeal cytokine elimination as rescue therapy in refractory septic shock: a prospective single-center study. *J Artif Organs* 2017; 20: 252-259.
- [22] Trager K, Skrabal C, Fischer G, et al: Hemoadsorption treatment of patients with acute infective endocarditis during surgery with cardiopulmonary bypass - a case series. *Int J Artif Organs* 2017; 40: 240-249.
- [24] David S, Thamm K, Schmidt BMW, et al: Effect of extracorporeal cytokine removal on vascular barrier functioning a septic shock patient. *J Intensive Care* 2017; 5: 12.
- [25] Hinz B, Jauch O, Noky T, et al: CytoSorb, a novel therapeutic approach for patients with septic shock: a case report. *Int J Artif Organs* 2015; 38: 461-4.
- [26] Trager K, Schutz C, Fischer G, et al: Cytokine Reduction in the Setting of an ARDS-Associated Inflammatory Response with Multiple Organ Failure. *Case Rep Crit Care* 2016; 9852073.].
- [27] Kogelmann K, Jarczak D, Scheller M, et al: Hemoadsorption by CytoSorb in septic patients: a case series. *Crit Care* 2017; 21: 74.
- [28] Kumar A, Roberts D, Wood KE, et al: Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med* 2006; 34: 1589-96.
- [29] Rivers E, Nguyen B, Havstad S, et al: Early Goal-Directed.
- [30] Therapy Collaborative Group. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001; 345: 1368-77.
- [31] Kohei Nagumo, Motohiko Tanaka, Victor Tuan Giam Chuang, Hiroko Setoyama, Hiroshi Watanabe, Naoyuki Yamada, Kazuyuki Kubota, Motoko Tanaka, Kazutaka Matsushita, Akira Yoshida Hideaki Jinnouchi, Makoto Anraku, Daisuke Kadowaki, Yu Ishima, Yutaka Sasaki, Masaki Otagiri and Toru Maruyama; Cysteinylated Human Serum Albumin Is a Sensitive Plasma Marker in Oxidative Stress-Related Chronic Diseases; *PLoS One*. 2014; 9 (1): e85216. Published online 2014 Jan 8. doi: 10.1371/journal.pone.0085216PMCID: PMC3885702PMID: 24416365Cys34.
- [32] Del Giudice, Dicko, Galantini; Structural response of Human Albumin to Oxidation: Biological Buffer to local formation of Hypochlorite; Pavel-Boeringer-2019.
- [33] Caironi P, Tognoni G, Masson S, Fumagalli R, Pesenti A, Romero, Fanizza C, Caspani L, Faenza S, Grasselli G, Iapichino G, Antonelli M, Parrini V, Fiore G, Latini R and Gattinoni L for the ALBIOS Study Investigators. Albumin Replacement in Patients with severe Sepsis or Septic Shock. *N Engl J Med* 2014.