# Successful Use of HA380 Filter in a Kidney Transplant Patient with Septic Shock

Nefrologo in corsia

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**ABSTRACT**
Septic shock is a high-risk disease secondary to infections by pathogens, often rapidly evolving and requiring complex treatment. Dysregulation of the immune response can lead to organ hypoperfusion, multiorgan failure and death.
In this context, multiple studies are being conducted to find new therapeutic strategies that can improve prognosis. Among these, hemoperfusion techniques using adsorbent filters have emerged.
In this paper, we describe our experience in the treatment of septic shock in a kidney transplant patient.

**PAROLE CHIAVE**: hemoperfusion, sepsis, kidney transplant

## Introduction

Septic shock is a severe and life-threatening condition characterized by a dysregulated host response to infection, leading to widespread tissue hypoperfusion, organ dysfunction, and, ultimately, increased mortality. The incidence of septic shock remains high, representing the main reasons for patients admitting to intensive care units (ICUs) in Europe. Early recognition and prompt intervention are crucial for improving outcomes in septic shock patients [1].

Traditional therapy for septic shock is based on rehydration, early administration of broad-spectrum antibiotics, control of the inciting cause (e.g., surgical drainage of abscesses), and measures to ensure hemodynamic stability. Vasopressor agents are often used to maintain mean arterial pressure (MAP) above 65 mmHg [1].

The potential role of hemoperfusion in the management of septic shock has recently been explored. Hemoperfusion involves passing blood through an adsorbent material to remove toxins and proinflammatory factors from the bloodstream. This technique has shown encouraging results in reducing the levels of circulating endotoxins and cytokines, which are major determinants of the inflammatory response in septic shock [2].

Septic shock continues to represent a significant challenge in intensive care medicine, with high incidence and mortality rates [3]. While classic treatments attempt to provide basic management, the exploration of new therapies such as hemoperfusion offers hope for improving patient outcomes.

In this context, we report a clinical case in which hemoperfusion techniques have been applied in the treatment of septic state.

## Case report

A 79-year-old male was admitted to the Emergency Department anuric and drowsy, with fever associated with chills (body temperature 39.4°C) and seizures. He also showed arterial hypotension, bradycardia and dyspnea with low oxygen saturation levels.

He had a history of arterial hypertension; acute myocardial infarction (AMI) undergone to revascularization with percutaneous coronary intervention (PCI) and stenting (2001 and 2014); ADPKD (1992) with resulting ESRD (2008) treated with hemodialysis through arteriovenous fistula; right nephrectomy (2011); deceased-donor kidney transplant in right iliac fossa (2012); left nephrectomy and splenectomy (2015); toxic multinodular goiter, recurrent deep vein thrombosis, previous hepatitis B virus (HBV) infection.

At admission blood tests showed normal white blood cells count, CRP 1.64 mg/dl, PCT 98.3 ng/ml, creatinine 3.98 mg/dl, urea 91 mg/dl, normal electrolytes, BNP 4430.90 pg/ml. A brain and abdomen CT scans showed no alterations, while signs of lung congestion emerged at a chest CT scan. An electrocardiogram (EKG) documented a third-degree atrioventricular block. A transthoracic echocardiogram showed biventricular dilation with preserved EF and no other alterations of interest. Thus, he was transferred to the Cardiac Intensive Care Unit.

Virological tests, such as the search for polyomavirus, CMV and EBV DNA, resulted in negative. Blood and urine cultures were collected, and the blood samples later showed the presence of Escherichia coli.

Meanwhile, fluid therapy, diuretics, vasopressors, broad spectrum antibiotics, antifungal therapy and oxygen therapy were started, and a temporary transcutaneous pacing was placed; the

immunosuppressive therapy was modified discontinuing everolimus and introducing tacrolimus; due to persistent anuria a central venous catheter was inserted, and continuous renal replacement therapy (CRRT) was started.

Despite all these therapeutic measures, the clinical status remained unchanged and lab tests worsened with a further increase of CRP (25.34 mg/dl) and PCT (274 ng/ml) associated to neutrophilic leukocytosis; so, the patient underwent a session of hemoperfusion combined with continuous venovenous haemodialysis (CVVHD); CVVHD was performed using EMIC filter and the session was carried out in series with Jafron HA 380 cartridge. The session lasted almost nine hours using citrate anticoagulation and the following parameters: Qb 150 ml/min, Qd 2000 ml/h, UF 200 ml/h. Blood count test, CRP, PCT and IL-6 were measured before and after the treatment and they all showed a decreasing trend (Table 1); only IL-6 a few days later showed a further mild increase (Figure 1).

After the treatment a regression of the complete heart block was also observed so that the implantation of a cardiac pacing became unnecessary. Thanks to the improvement of hemodynamic parameters noradrenaline was discontinued. Over time the restoration of diuresis allowed discontinuation of hemodyalisis too. Laboratory tests performed one week after the acute episode showed a stabilization of renal function on creatinine values equal to 1.6 mg/dL. Then the patient was discharged home in improved and stable clinical conditions; unfortunately, he suddenly died a few months later.

| Parameters | At the time of admission | T0 before treatment | T1 after treatment | T2 a day after treatment |
|---|---|---|---|---|
| CRP mg/dl | 1.64 | 25.34 | 11 | 7 |
| PCT ng/ml | 98.3 | 274 | 98 | 70 |
| IL 6 pg/ml | / | 99 | 51 | 71 |
| Creatinine mg/dl | 1.64 | 3.98 | / | 1.2 |

Table 1. Trend of values before and after treatment whit HA 380 cartridge.

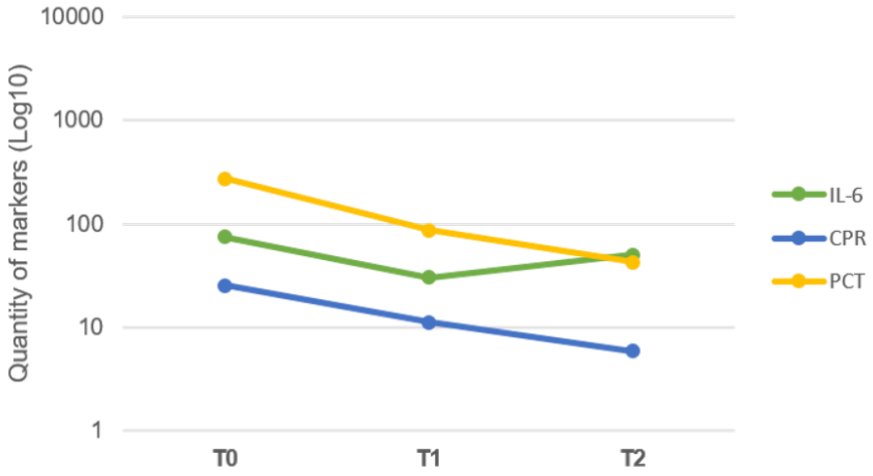


Figure 1. Evaluation of inflammatory indices before and after treatment with HA 380 cartridge.

## Discussion

Sepsis and septic shock are complex healthcare challenges, affecting millions of people worldwide each year and resulting in a mortality rate of one in three to one in six cases. Early diagnosis and optimal management during the first hours of presentation can positively influence the prognosis of

patients [1]. Sepsis is defined as life-threatening organ dysfunction caused by an uncontrolled host response to infection, highlighting the criticality of the unregulated host response and the urgent need for rapid diagnosis and treatment [4].

The infection process begins when the immune system recognizes a possible pathogen. Pathogens present specific components on their surface called pathogen-associated molecular patterns (PAMPs), such as endotoxins present in Gram-negative bacteria [5]. PAMPs are recognized by pattern recognition receptors on immune cells, triggering leukocyte activation and release of cytokines such as tumor necrosis factor alpha, interleukins (IL-1, IL-6, IL-8, IL-10), which drives the immune response [6].
The massive release of cytokines, often referred to as a "cytokine storm", is associated with major organ dysfunction in sepsis [7]. In addition, damaged host cells release damage-associated molecular patterns (DAMPs), such as high-mobility-group-box-1 (HMGB1), resulting in further immune activation and maintenance of the inflammatory process [8].
Following the cytokine storm, a state of immunoparalysis can develop, leading to an increased risk of secondary infections and contributing to sepsis-related mortality [9].

The principles of treatment for sepsis include fluid resuscitation, hemodynamic support, antibiotics, and source control [10]. Extracorporeal blood purification has emerged as an additional therapy, although current guidelines do not provide specific recommendations due to insufficient evidence [11]. Extracorporeal blood purification can be achieved by convection, diffusion, or adsorption processes. Various membranes and adsorbent cartridges are used, each with distinctive characteristics. Hemoperfusion (HP) involves passing blood through a cartridge containing adsorbent materials, which can selectively remove toxins, cytokines, and other inflammatory mediators. There are two main approaches in this context: selective and nonselective adsorption.

1. Selective adsorption. This technique targets specific molecules, such as endotoxins, using cartridges such as those containing polymyxin B. These systems find their main use in gram-negative sepsis where endotoxins play a key role.
   However, the clinical efficacy of these systems remains under investigation, with some studies showing limited benefits in improving patient outcomes [2, 12]. Semiselective membranes like the AN69 oXiris membrane have enhanced adsorptive capacities for endotoxins and inflammatory mediators, while selective cartridges like the ToraymyxinTM cartridge specifically target endotoxins without removing cytokines [13].
   Other devices, such as the JAFRON HA cartridge and Seraph® 100 Microbind® Affinity Blood Filter, have demonstrated efficacy in reducing inflammation and improving clinical outcomes in critically ill patients [14, 15].

2. Non-Selective Adsorption. Nonselective membranes, such as highly adsorptive membranes (HAMs), remove mediators and substances below the 35 kDa range. For instance, the acrylonitrile 69 surface-treated (AN69 ST) membrane removes cytokines, antibiotics, and lactate but is ineffective against endotoxins [16]. The polymethylmethacrylate (PMMA) filter, used in continuous veno-venous hemofiltration (CVVH), exhibits greater adsorption capacity and removes cytokines and HMGB1 [17]. The CytoSorb device, which consists of porous resin beads, can remove molecules in the 5-60 kDa range, including cytokines and bacterial toxins; however, it cannot remove endotoxins [14]. This broad-spectrum approach may offer advantages in sepsis, where multiple cytokines and toxins drive disease progression. While early clinical experience with devices such as CytoSorb is promising, showing reductions in cytokine levels and improvements in hemodynamics, large-scale randomized clinical trials that can definitively describe their efficacy have not yet been conducted [18, 19].
   In addition to hemoperfusion, high-cutoff (HCO) membranes used in continuous renal

replacement therapy (CRRT) have been studied for their ability to remove larger molecules, such as cytokines, from the circulation. These membranes, which have larger pore sizes than conventional high-flux membranes, allow for the removal of molecules up to 60 kDa. Although HCO membranes have shown the ability to reduce inflammation and improve patient outcomes in early studies, their widespread adoption is limited by concerns about excessive albumin loss and the lack of consistent clinical benefits across patient populations [18, 19].

The clinical application of these technologies in the management of sepsis is still in its infancy. While some small-scale studies and case reports indicate potential benefits, such as improved hemodynamics and reduced need for vasopressor agents, larger, well-designed studies are needed to establish their efficacy and safety profiles. The heterogeneity of sepsis presentations, variability in patient responses, and the need to attempt to standardize treatment protocols complicate the evaluation of these therapies [16, 18].

**Conclusion**

In this paper we report a case in which HP with JAFRON HA 380 proved to be effective during severe septic shock, allowing interruption of amines, resumption of diuresis and resolution of third-degree atrioventricular block. Although HP is a promising technique, there are no established guidelines for hemoperfusion, but several biologically and pathophysiological rational indications can be identified:

- intoxication either with a drug, like valproate and carbamazepine, or toxic chemical, like paraquat and organophosphates, or toxic natural products, like mushroom-related toxins;
- liver disease: data are limited for severe liver failure, either acute or acute on chronic, even if ammonia or bilirubin might be potential targets; a possible application of HP could be also intractable cholestatic pruritus;
- renal disease: there is a variety of end-stage renal failure-associated toxins, such as beta-2 microglobulin, not adequately removed during dialysis justifying the combined use of resins in selected patients or uremic pruritus;
- sepsis: two approaches have been developed, one based on selective targeting of a key molecule, like endotoxin, and supported by several trials, the other based on non-selective adsorption, not yet tested in suitably designed multicenter randomized trials.

Haemadsorption therapy has several limitations that hinder its wider clinical use, as highlighted in the scientific literature. One of the main difficulties is the heterogeneity of patients admitted to the ICU, which makes it difficult to identify those who could actually benefit from this treatment.

The most recent guidelines of the Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock (2016) do not include specific recommendations on the use of blood purification techniques in patients with sepsis. Furthermore, the indications for initiating renal replacement therapy (RRT) in sepsis-associated AKI remain unchanged compared to those of AKI resulting from other causes. The adoption of particular adsorbent techniques can be evaluated as an adjunctive treatment, taking each case into consideration.

The lack of definitive evidence regarding clinical outcomes is not surprising, since several randomized controlled trials conducted in recent years, aimed at evaluating various interventions in critically ill patients, with or without sepsis, have not shown any significant benefit on survival. This highlights the complexity of evaluating the effectiveness of interventions in large cohorts characterized by significant clinical variability.

Therefore, to better define the indications and the timing of intervention there is a need for further studies.

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