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oXiris® Use in Septic Shock: Experience of Two French Centres

Victor Schwindenhammer[a] Thibaut Girardot[a, b] Kevin Chaulier[c]
Arnaud Grégoire[a] Céline Monard[a] Laetitia Huriaux[a] Julien Illinger[c]
Véronique Leray[a] Thomas Uberti[a] Jullien Crozon-Clauzel[a]
Thomas Rimmelé[a, b]

[a]Anaesthesia and Critical Care Medicine Department, Edouard Herriot Hospital, Hospices Civils de Lyon, Lyon, France; [b]EA 7426 PI3 (Pathophysiology of Injury-Induced Immunosuppression), Claude Bernard University Lyon 1-bioMérieux-Hospices Civils de Lyon, Lyon, France; [c]Intensive Care Unit, L'Hôpital Nord-Ouest, Villefranche-sur-Saône General Hospital, Gleizé, France

Keywords
Blood purification · Haemoadsorption · oXiris® · Renal replacement therapy · Sepsis · Septic shock

Abstract
Background: Sepsis is a dysregulated host response to an infection and can result in organ dysfunctions and death. Extracorporeal blood purification techniques aim to improve the prognosis of these patients by modulating the unbalanced immune response. This study reports our experience with the use of the oXiris® membrane for septic shock patients requiring continuous renal replacement therapy (CRRT). ***Summary:*** Thirty-one patients were diagnosed with septic shock and underwent CRRT with the oXiris® membrane between 2014 and 2019. We compared the observed hospital mortality with that predicted by the Simplified Acute Physiology Score II (SAPS II). Change in the Sequential Organ Failure Assessment (SOFA) score and of the main clinical and biological parameters over time were analyzed. Hospital mortality was lower than predicted for the most severe patients (60 vs. 91% for the [74–87] SAPS II quartile and 70 vs. 98% for the [87–163] SAPS II quartile, $p < 0.02$). There was no significant improvement in the SOFA score from 0h to 48 h. An 88% relative decrease in norepinephrine infusion was observed (median at 0 h was 1.69 [0.52–2.45] µg/kg/min; at 48 h it was 0.20 [0.09–1.14] µg/kg/min, $p = 0.002$). Lactataemia and pH were significantly improved over time. Patients with intra-abdominal sepsis as well as those with Gram-negative bacilli (GNB) infections seemed to benefit the most from the therapy. ***Key Messages:*** CRRT with the oXiris® haemofilter resulted in higher observed survival than predicted by a severity score (SAPS II) for the most severe patients. Haemodynamic status and lactataemia appeared to improve, especially in intra-abdominal sepsis and GNB infections.

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E-Mail karger@karger.com
www.karger.com/bpu

Thibaut Girardot, MD
Service d'anesthésie-réanimation
Hôpital Edouard Herriot
5, place d'Arsonval, FR–69457 Lyon Cedex 03 (France)
E-Mail thibaut.girardot@chu-lyon.fr

Introduction

Sepsis is one of the leading causes of morbidity and mortality in intensive care units (ICU). It is estimated that there are 19 million cases of septic syndromes worldwide annually, causing about 5 million deaths [1]. Acute kidney injury (AKI) occurs in about 50% of patients treated for a septic shock and is associated with a higher mortality [2]. The consequences of sepsis persist in the long term, survivors having an increased risk of cardiovascular events compared to age-, sex-, and comorbidity-matched hospitalised subjects without organ dysfunction [3].

From a pathophysiological point of view, sepsis is a dysregulated immune response to an infection, resulting in life-threatening organ dysfunctions. It is now widely accepted that pathogen-associated molecular patterns, such as endotoxins that are recognized by the host immune system, cause a significant increase in pro- and anti-inflammatory cytokines [4]. This cytokine storm in the acute phase of sepsis is responsible for shock, organ failure and secondary immunoparalysis [5]. Extracorporeal blood purification techniques have been developed to modulate the sepsis-induced immune response in order to limit its deleterious effects. The literature concerning endotoxin and cytokine removing techniques is heterogeneous; some studies found benefits on mortality [6], whereas others did not find any significant benefits [7]. Because of these discrepancies, the Surviving Sepsis Campaign makes no recommendation regarding the use of blood purification techniques [8].

Some haemofilters have been optimised to adsorb endotoxins and cytokines while also ensuring renal replacement therapy (RRT). The oXiris® haemofilter is a high permeability polyacrylonitrile (AN69)-based membrane, on which a positively charged polyethyleneimine surface treatment has been added. This allows the membrane to adsorb endotoxins (negatively charged) at the surface [9] in addition to cytokine elimination in the bulk of the membrane [10]. This membrane can be used either in continuous veno-venous haemofiltration (CVVH) or continuous veno-venous haemodiafiltration (CVVHDF). The oXiris® membrane is one of the available blood purification devices with the highest adsorption capacities for both endotoxins and cytokines [11]. However, to date, published evidence for its effectiveness is limited, and there is no recommendation for its clinical use. Animal studies found haemodynamic improvement in septic pigs [12] and decreased mortality in septic rats [13]. In human case series, an improvement in the haemodynamic status of septic shock patients treated with oXiris® was also observed [9, 10]. In addition, Shum et al. [14] found a 37% reduction in the Sequential Organ Failure Assessment (SOFA) score after 48 h of blood purification with the oXiris® membrane, compared to severity-matched historical controls undergoing standard RRT; Adamik et al. [9] found similar results with a decrease in the SOFA score from 14 to 7 in 72 h.

We hereby present our experience in the use of the oXiris® membrane for septic shock patients requiring continuous renal replacement therapy (CRRT). We sought to determine the change over time of clinical and biological parameters in septic shock patients treated with oXiris®. We also investigated the difference between observed and Simplified Acute Physiology Score II (SAPS II)-predicted mortality in this population.

Methods

This study was a retrospective cohort conducted in two French ICUs (one in a university hospital and the other in a general hospital). All patients who were diagnosed with septic shock and hospitalised in the ICUs between December 3, 2014, and January 5, 2019, and who underwent CRRT with the oXiris® membrane, were included in the study. All data were obtained from the hospitalisation records and the computerised monitoring sheets recorded on the ICU medical software. According to French legislation, this study was approved by the Ethics Committee of the Lyon teaching hospitals (*Hospices Civils de Lyon*) and declared to the French national data protection commission (*Commission Nationale de l'Informatique et des Libertés*, CNIL).

Demographic data (age, gender, body mass index), localisation of infection and identification of infectious agent were recorded, as well as the SOFA score at the moment the RRT session with the oXiris® membrane was initiated (0 h), as well as 24 and 48 h thereafter. We sought every bacterial samples made (haemoculture, respiratory, surgical, lumbar puncture, etc.) and recorded every infectious agent found. Haemodynamic, respiratory and biological parameters were also collected at the same time-points, as well as norepinephrine doses. Various RRT parameters were recorded, such as the RRT modality (CVVH or CVVHDF), the prescribed dialysis dose, the type of anticoagulation (citrate, heparin, or none), the total duration of RRT during the ICU stay, the number of sessions performed with the oXiris® membrane and the duration of each session with this haemofilter. The interval between ICU admission and initiation of blood purification with the oXiris® membrane was also recorded. In addition, observed hospital mortality was compared to that predicted by the SAPS II. SAPS II estimates mortality in ICU patients using several clinical and biological parameters.

The Shapiro-Wilk test found non-Gaussian distribution for most parameters; continuous data are reported as medians (interquartile range [IQR]), and differences explored using non-parametric Wilcoxon tests. Kruskal-Wallis tests were used for multiple group comparisons, and post hoc Nemenyi test when needed. Comparison between observed and expected mortality used the W-statistic [15].

Results

A total of 31 patients were included, and these underwent a total of 42 CRRT sessions. The median (IQR) SAPS II score was 74 (52–87), and the median (IQR) SOFA score was 14 (11–16). Treatment with oXiris® was initiated 25 (8–75) h after ICU admission, and the median session duration was 17 (5–54) h. The main infectious site was intra-abdominal (43%), and Gram-negative bacilli (GNB) were identified in 50% of cases (Table 1). Other demographic data are reported in Table 1.

Hospital mortality was 64.5% (20/31), but lower than predicted by the SAPS II. Compared to mortality predicted by SAPS II, there were 9.2% unexpected survivors, although this difference did not reach statistical significance ($p = 0.136$). According to the gravity quartiles, there was no significant difference in time between ICU admission and first use of the oXiris® membrane. A significant difference between observed and predicted mortality was observed in patients with a SAPS II greater than 74 (predicted mortality >88%; Table 2).

No significant improvement in the SOFA score was observed 24 or 48 h after RRT initiation. Haemodynamic status was significantly improved; there was an 88% relative decrease in the median (IQR) norepinephrine dose from RRT initiation (1.69 [0.52–2.45] μg/kg/min) to 48 h thereafter (0.20 [0.09–1.14] μg/kg/min, $p = 0.0025$; Fig. 1). pH and lactataemia were also significantly improved at 48 h (respectively from 7.26 [7.18–7.34] to 7.43 [7.42–7.49], $p < 0.00001$, and from 6.8 [3.1–12.6] to 1.7 [1.3–3.5], $p = 0.0006$; Fig. 1). PaO_2/FiO_2 ratio, platelets and diuresis were not modified during oXiris® sessions.

In the subgroup with abdominal sepsis, there was no significant difference in hospital mortality or in SOFA score from initiation of RTT to 48 h thereafter, compared with other types of infection. In this subgroup, there was a significant decrease in lactataemia, and in those with extra-abdominal sepsis, the decrease was not significant (Fig. 2). There was no significant difference between these two groups for the other criteria (mean arterial pressure, norepinephrine requirements, pH). In patients for whom a GNB was identified, no significant improvement in the SOFA score was found at the different time-points. Like in the abdominal infection subgroup, we observed a significant decrease in lactataemia that was not seen for other infectious agents (Fig. 2). There was also a haemodynamic improvement with a significant increase in mean arterial pressure and a trend towards a decrease in norepinephrine requirements in this GNB subgroup 48 h after RRT initiation.

Table 1. Description of the population included

Demographic characteristics	
Number of sessions	42
Number of patients	31
Age, years	65 (54–72)
Gender, male	30 (71)
BMI, kg/m^2	26 (23–33)
SAPS II	74 (52–87)
SOFA	14 (11–16)
Norepinephrine, μg/kg/min	1.7 (0.5–2.4)
Mechanical ventilation	41 (98)
PaO_2/FiO_2 ratio	153 (92–236)
pH	7.26 (7.18–7.34)
Lactate, mmol/L	6.8 (3.1–12.6)
RRT parameters	
RRT modality	
CVVH	17 (40)
CVVHDF	25 (60)
Circuit anticoagulation	
Citrate	17 (40)
Heparin	13 (31)
None	12 (29)
KDIGO stage before RRT initiation	3 (3–3)
Prescribed dialysis dose, mL/kg/h	42 (36–49)
Time between ICU admission and oXiris® initiation, h	25 (8–75)
Number of sessions per patient	1 (1–2)
Session duration, h	17 (5–54)
Infection characteristics	
Site of infection	
Abdominal	18 (43)
Pulmonary	14 (33)
Urinary	3 (7)
Others	7 (17)
GNB identified	21 (50)
Positive blood culture	21 (50)

Data are expressed as median (IQR) for continuous data and number (%) for categorical data.

GNB, Gram-negative bacilli; SOFA, sequential organ failure assessment; RRT, renal replacement therapy; CVVH, continuous veno-venous haemofiltration; CVVHDF, continuous veno-venous haemodiafiltration; ICU, intensive care unit.

Table 2. Comparison of observed and predicted mortality according to SAPS II quartiles

SAPS II quartile	0–51	52–73	74–86	87–163
Number of patients	6	10	5	10
W-statistic, %	–23.09	–0.95	31.25	27.66
p value	0.193	0.945	0.013	<0.0001

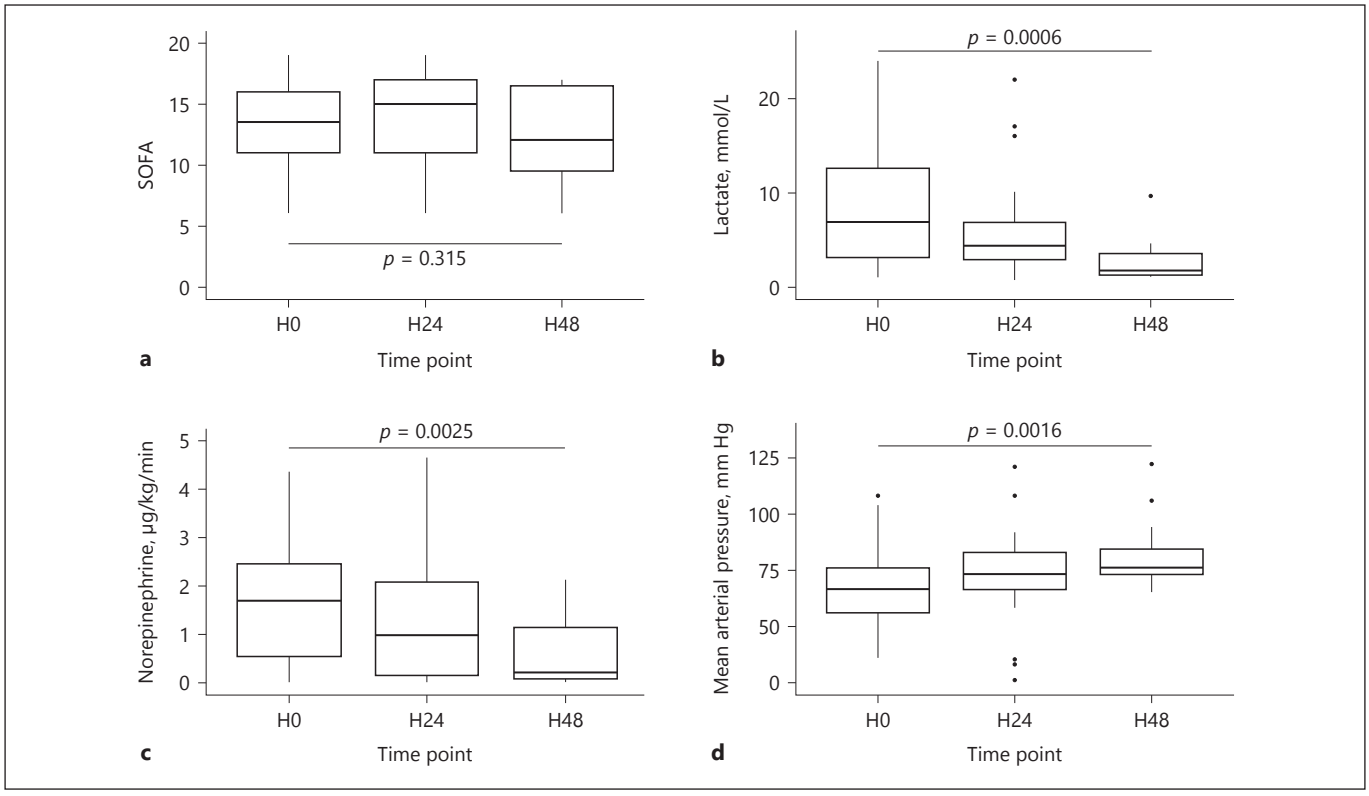

Fig. 1. Change over time of the main parameters. SOFA score (**a**), lactataemia (**b**) norepinephrine dosage (**c**), and mean arterial pressure (**d**) are presented as Tukey boxplots: the horizontal line represents the median value, box extremities represent the first and third quartiles, and whiskers represent the lowest or highest value still within 1.5 IQR of the lower or higher quartile, respectively; dots denote outliers. SOFA, Sequential Organ Failure Assessment.

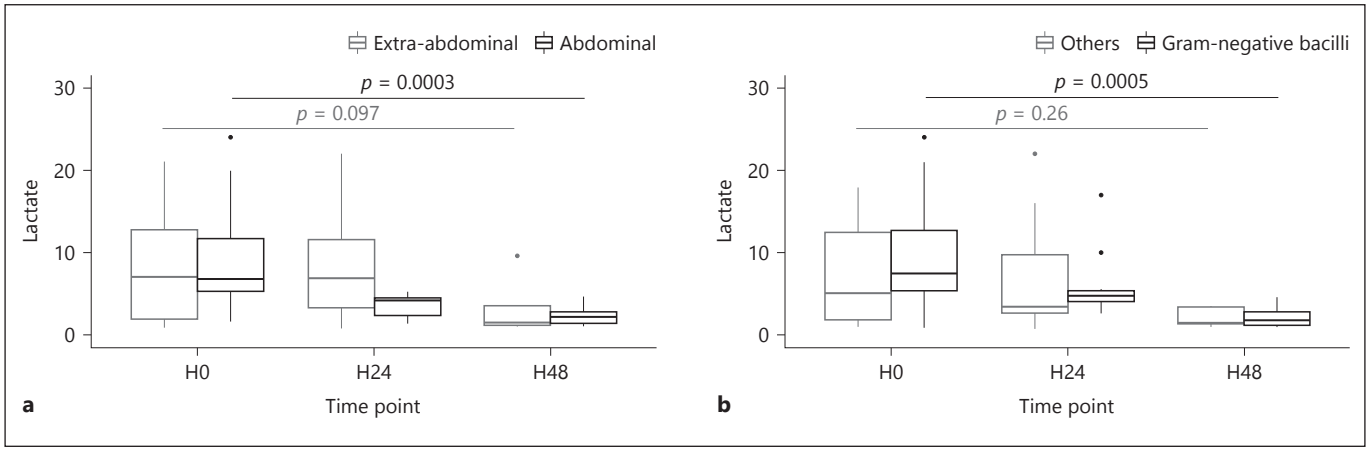

Fig. 2. Change over time of lactataemia according to infection site and bacteria. Lactataemia according to infection site (**a**) and bacteria (**b**) are presented as Tukey boxplots: the horizontal line represents the median value, box extremities represent the first and third quartiles, and whiskers extremities represent the lowest or highest value still within 1.5 IQR of the lower or higher quartile, respectively; dots denote outliers.

Discussion

In this retrospective cohort study, the use of the oXiris® membrane for RRT in patients with septic shock and AKI was associated with a survival benefit for the most severe patients.

Despite appropriate management (early and adequate antibiotics, source control by surgery whenever possible), septic shock-associated mortality remains very high, particularly in case of sepsis-associated AKI [2]. Sepsis causes a major systemic inflammatory state that is part of the physiological reaction to infection. However, this inflammatory response can also be uncontrolled, causing excessive or unbalanced production of inflammatory cytokines [4], potentially resulting in organ dysfunction and death. Furthermore, prolonged production of anti-inflammatory mediators may lead to a profound immunosuppression state, sometimes named immunoparalysis, during which most of the sepsis-associated mortality is observed [5]. Extracorporeal blood purification could therefore be an additional asset for clinicians, as its principle is to mitigate this pro- and anti-inflammatory overflow. Several theories exist to explain the value of blood purification in sepsis, including the "cytokine peak hypothesis" [16], the "threshold immunomodulation theory" [17], the "cytokinetic model" [18] and the modulation of immune cells themselves [19].

Various blood purification techniques have been developed during the past decades, but to date, results from multicentre randomized controlled trials have been disappointing. High-volume haemofiltration has not shown any benefit on mortality, or length of hospital stay in high quality trials [20]. In the same way, despite promising initial results [6], the use of polymyxin B-immobilised fibre column for haemoperfusion in sepsis is still debated [7, 21]. Furthermore, Coupled Plasma Filtration and Adsorption is no longer recommended for patients suffering from septic shock because of an increase in early mortality observed in the COMPACT-2 study (results not published to date). Another disadvantage of all these techniques (apart from high volume haemofiltration) is that they do not allow renal support, whereas ICU patients regularly develop AKI [22]. Thus, RRT membranes optimization, such as increasing the adsorptive capacities, could be an interesting alternative blood purification option and is the rationale for using the oXiris® haemofilter, which can remove both endotoxins and cytokines [11] while providing RRT.

We report herein a haemodynamic improvement illustrated by a significant reduction of norepinephrine needs during the first 48 h of oXiris® treatment. These results concur with most studies that have investigated the oXiris® filter [9, 14, 23]. This improvement seems to be greater using oXiris® membrane, rather than another RRT filter without endotoxins or cytokines adsorption quality [23]. Other studies found a significant decrease in the SOFA score with oXiris® [9, 14], but this was not observed herein. One hypothesis is that our patients were very severe with a high mortality. Thus, they potentially needed longer care and we could have observed an improvement in the SOFA score later than 48 h after the initiation of the oXiris® therapy. In the present cohort, half of patients had GNB, and nearly half suffered from intra-abdominal sepsis. As the oXiris® membrane is to eliminate endotoxins, one could hypothesize that it would not be as effective in infections secondary to other types of bacteria. The results are consistent with this hypothesis and other studies. Indeed, Tang et al. [24] suggested that improvements in vasopressor requirements and lactataemia could occur later in Gram-positive infections. Tang et al. [25] observed rapid shock reversal in patients with intra-abdominal sepsis treated by oXiris® compared to patients who received ordinary haemodiafiltration. Likewise, we obtained significant results on lactate clearance in the intra-abdominal infections and GNB subgroups. This is also concordant with animal studies [12], and it is of note that patients infected with GNB appeared to benefit the most from this membrane in the present study. However, septic shock is often caused by polymicrobial infections; in particular, intra-abdominal infections can involve both Gram-negative and Gram-positive bacteria. Thus, the removal of both cytokines and endotoxins could be complementary in this context. It is also possible that the timing of blood purification with the oXiris® membrane is an important factor. For instance, Govil et al. [26] found that septic patients who underwent oXiris®-based RRT within 3 h of achieving adequate fluid resuscitation had better outcomes than those in whom oXiris® was used as a last resort. In the early group, the authors observed greater improvements in the SOFA score and vasopressor reduction [26]. In a retrospective case series, Tang et al. [24] highlighted that survivors had shorter mean time to oXiris® initiation compared with non-survivors (7.2 vs. 12.5 h). In our experience, patients benefited from an oXiris® session relatively late (median: 25 h) after their admission to the ICU. Indeed, our patients benefited of RRT at an advanced AKI stage, and they were therefore treated at this moment by the oXiris® therapy. This time before oXiris® initiation in our study can also explain the lack of significant improvement in the SOFA score.

The main limitation of the present study is its retrospective design and the relatively small number of subjects. However, no large cohort reporting the use of oXiris® in septic shock patients has been published to date. Second, this is a cohort study with no control group, and we therefore compared observed mortality to its prediction by a severity score. Third, the population was heterogeneous. Given the innovative nature of this technology and the few human data available, there is currently no consensus about its indications. Thus, we use this membrane in two main situations; the first to treat quite stable patient suffering from a sepsis-associated AKI. Conversely, the other possibility is to use it as rescue therapy for extremely severe patients. As a result, the inclusion of patients in the two ICU was not homogeneous, with some quite stable patients and some extremely severe patients. However, it reflects the current practice with this membrane today. Ongoing human randomized controlled trials are currently assessing the oXiris® membrane, compared to standard membranes (ECRO study, NCT03426943; oXiris study, NCT02600312), or to polymyxin B (ENDoX study, NCT01948778). The results of these studies will give more information on the oXiris® indications in the upcoming years.

Conclusion

Herein, CRRT with the oXiris® haemofilter resulted in survival that was better than predicted by a severity score (SAPS II) for the most severe patients. Moreover, the haemodynamic status appeared to improve rapidly, and lactataemia to decrease, in particular in those with intra-abdominal infection or GNB infections. Several ongoing studies are expected to clarify the use of this therapy.

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Disclosure Statement

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