

Extracorporeal Blood Purification with the oXiris® Filter for Patients with Sepsis and Hyperinflammatory Conditions: The Asia-Pacific oXiris Expert Meeting 2024 Consensus Statements.

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(<https://karger.com/Services/OpenAccessLicense>). Usage and distribution for commercial purposes requires written permission. Abstract Extracorporeal blood purification is a technique for reducing elevated levels of inflammatory mediators and/or endotoxins in critically ill patients with sepsis or other hyperinflammatory conditions. The oXiris filter combines endotoxin adsorption, cytokine adsorption, hemofiltration, and anti-thrombosis, and an emerging body of evidence demonstrates its use in critical care patients with hyperinflammatory conditions and acute kidney injury (AKI). A group of Asia-Pacific experts convened to formulate consensus statements for the use of the oXiris filter based on a comprehensive review of publications. After evaluation using a Delphi methodology, 17 statements achieved consensus (three recommendations and 14 practice points). These offer guidance on the initiation, monitoring, and evaluation of treatment with the oXiris filter in patients with sepsis, septic shock, severe COVID-19, or other hyperinflammatory states. We also recommend using the oXiris filter in patients undergoing cardiopulmonary bypass for cardiac surgery who are at risk for developing AKI. Other statements discuss modality, dosage, filter lifespan, anticoagulation, and combining the oXiris filter set with other extracorporeal therapies. Taken together, our statements offer targeted guidance for clinicians on the use of the oXiris filter across different patient populations. Additionally, we highlight the limitations of the current evidence base and identify key areas requiring further research.

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WCAG 2.1 Level AA accessibility-pdf-ua-compliance yes Introduction Sepsis is a life-threatening condition resulting from a dysregulated host response to infection, leading to upregulation of pro-inflammatory cytokines, endothelial injury and extravasation, hypercoagulability, thrombocytopenia, and myelopoiesis [1 , 2]. Endotoxin – components of the cell wall of Gram-negative bacteria – also plays an important role in the inflammatory cascade that occurs during sepsis [3]. Furthermore, hyperinflammatory states with immunopathogenic mechanisms similar to sepsis have been described in patients with other severe illnesses, including severe COVID-19 and other causes of acute respiratory distress syndromes [4], serious burn injuries [5], and severe acute pancreatitis [6]. Sepsis and noninfectious sources of inflammation may lead to acute kidney injury (AKI), and AKI may exacerbate inflammation from other causes by impairing cytokine clearance [7].

Conventional therapies for sepsis include fluid resuscitation, source control, and antimicrobial administration [2 , 8]. Extracorporeal blood purification (EBP) is an emerging technique for patients with hyperinflammation where blood is removed from the body and treated with various filtration and adsorption technologies before being returned to the patient [9]. The aim of EBP is to reduce the circulating levels of inflammatory mediators such as cytokines and endotoxins to restore immune balance [10]. Different forms of EBP have been developed, including hemofiltration, intermittent or continuous high-volume hemofiltration, hemoadsorption, and plasmapheresis [10].

The oXiris ® filter is a hemofiltration device based on the acrylonitrile-co-methallyl sulfonate surface-treated (AN69ST) membrane with an enhanced linear polyethyleneimine coating and pre-grafted heparin that combines four functions in one device, namely, endotoxin adsorption, cytokine adsorption, hemofiltration, and local anti-thrombosis [9]. Clinical experience is emerging for the use of the oXiris filter in the critical care of patients with sepsis and hyperinflammatory conditions, notably severe COVID-19 infections [11]. Earlier publications have summarized expert experience and opinion regarding the use of the oXiris filter; however, these have tended to focus on either COVID-19 or sepsis populations only and, despite the high rates of EBP usage in the Asia-Pacific (APAC) region, reflect clinical experience in Europe and the USA [12 , 13].

A previous consensus publication from this APAC expert group was published in 2021, but this was focused on the use of the oXiris filter set for sepsis patients with AKI and predated the substantial experience gained using the oXiris filter set during the COVID-19 pandemic [14]. Since 2021, there have been many new publications reporting on clinical experience in APAC with the oXiris filter, including two meta-analyses [15 , 16]. This manuscript summarizes the results of a meeting of APAC experts to consolidate clinical evidence for the oXiris filter and formulate consensus statements on the use of the oXiris filter set in patients with sepsis and other hyperinflammatory conditions.

The Asia-Pacific oXiris Expert Group comprised senior intensivists and critical care nephrologists from nine APAC territories, with up to 10 years of direct clinical experience with oXiris filter treatment. These experts also have research interests in critical care and management of sepsis patients with AKI, with several of the participants being prior contributors to regional consensus, or principal or coinvestigators in oXiris-related trials, ensuring their practical and research proficiency. Additionally, two authors (M.W. and Q.Y.) are employees of Vantive Health LLC who assisted with requests from the authors for technical data related to oXiris, literature requests, and assisted in the drafting and critical revision of the manuscript. They did not participate in formulation of the consensus statements, the Delphi process, discussion of the finalized statements, or modification of the intellectual content of the manuscript. The development of this consensus occurred in three phases: pre-meeting, consensus meeting, and post-meeting.

During the pre-meeting phase, a series of clinical questions surrounding the oXiris filter use were identified and formulated using the Population, Intervention, Comparator, Outcome (PICO) framework, with feedback via an anonymous survey to guide the literature search and data extraction. These questions focused on the oXiris filter and did not consider other EBP filter types due to its unique mode of action, which would hinder the interpretation of the data. A comprehensive literature review was conducted on the use of oXiris filters in patients with sepsis, septic shock, or critical illnesses. Eleven databases of scientific publications and study registrations were systematically searched to collect all studies relevant to this topic as of March 2024. The included databases were Web of Science, the Cochrane Library, PubMed, EMBASE, the International Clinical Trials Registry Platform, ClinicalTrials.gov , the Wanfang Database, China National Knowledge Infrastructure, Sino-Med, VIP Database for Chinese Technical Periodicals, and the Chinese Clinical Trial Registry. Search terms used were “oXiris,” “cytokine storm,” “adsorptive hemofiltration,” “hemoperfusion,” “membrane adsorption,” “CRRT,” “extracorporeal blood purification,” and “sepsis/septic shock,” combined with “AND” and “OR.” Studies were excluded if they were duplicates of those already included, off-topic, or did not meet basic inclusion criteria. Considering that this consensus focuses on clinical practice guidance, animal studies were excluded from the evidence base for clinical questions 1–8 due to species-specific differences, limitations in clinical translation to humans, and their evidence hierarchy being lower than human studies. For clinical question 9, regarding antibiotic clearance mechanisms, animal and in vitro studies were included to supplement mechanistic evidence, as human in vivo studies are constrained by ethical issues and metabolic complexity, making it difficult to obtain data.

The literature search results were summarized, including the extraction of clinical data into summary tables, and used to formulate a set of draft consensus statements. The draft statements were initially evaluated using an online Delphi-based approach, using a 5-point Likert scale (agree – 5 points, agree with minor changes – 4 points, agree with major changes – 3 points, disagree with major changes – 2 points, completely disagree – 1 point). Proposed revisions to the statements were also gathered during this process. The results of the online evaluation and proposed revisions were presented and discussed at a consensus meeting in September 2024. During this meeting, statements were assessed using further rounds of the Delphi-based process. Agreement was defined as the level of consensus among advisors reaching $\geq 80\%$ agree or agree with minor changes, and an average score >4.50 points. Statements that did not achieve consensus were iteratively revised and reevaluated until consensus was achieved. If consensus could not be achieved for a draft statement after multiple rounds of evaluation, its discussion was used to

develop the explanatory text, as were discussions around the revision of statements for approval. A summary of voting results and the iterative revisions made to the statements is included in online supplementary material 1 (for all online suppl. material, see <https://doi.org/10.1159/000548214>).

Post-meeting, the consensus statements were classified as recommendations or practice points (PPs) based on the quality of evidence. A recommendation proposes a particular course of action based on evidence and expert opinion. The objective is to provide guidance for clinical practice and to enhance patient outcomes. The quality of evidence was rated for each of the recommendations using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach and the GradePro GDT tool (<https://www.grade-pro.org>). PPs are practical advice or tips derived from clinical experience and evidence. These points help clinicians implement recommendations in everyday practice. PPs are typically based on expert opinion and experience and lack the support of large-scale clinical studies. Quality of evidence grading has not been provided for PPs.

The post-meeting phase included the consideration of a randomized controlled trial (RCT) of oXiris filters (SIRAKIO2) [17] that was published shortly after the consensus meeting and used to formulate an additional statement. This additional statement and minor revisions to some of the statements approved during the meeting for language and clarity were discussed and evaluated online following the meeting. Modifications to statements were not substantive and were reviewed and approved by all authors.

A total of 99 publications were identified during the literature search, and a large, randomized study that was published shortly after the meeting was also included in the evidence base for analysis [17], yielding a total of 100 publications (online suppl. Figure). These included randomized studies (n = 9) [18 – 25], systematic reviews and/or meta-analyses [15 , 16 , 26 , 27], prospective studies (n = 14) [28 – 41], retrospective studies (n = 22) [42 – 63], and other real-world and registry studies (n = 11) [21 , 64 – 73]. The most frequently identified studies were case reports and case series (n = 26) [13 , 74 – 98]. Other publication types included an in vitro study [99], a consensus statement [12], narrative review [100], surveys, and other publication types [101 , 102]. Most studies were published; however, one preprint manuscript [35] and five masters or doctoral theses [25 , 33 , 54 , 62 , 64] were also included. Consensus among the experts was achieved for 17 statements (3 recommendations and 14 PPs); these are summarized in Table 1 and have been adapted as an algorithm (Fig. 1).

Hemodynamic instability with high-dose vasopressors (NE >0.5 µg/kg/min) or more than 2 vasopressors used after adequate fluid management

Sepsis-associated AKI mandating CRRT initiation

Persistent elevation of lactate levels, APACHE, or SOFA score

Increased commonly used inflammatory markers (white cell count, CRP, PCT)

Improvement in hemodynamic parameters with a reduction of vasoactive therapy (≥50% reduction) as early as 24 h

Improvement in clinical parameters (MAP/heart rate/PaO₂/FiO₂ ratio) after 24 h

Reduction in inflammatory biomarkers: lactate/CRP/PCT/IL-6 within 24 h

No improvement in hemodynamic parameters/dependence on vasopressors after 72 h

Pediatric patients with body weight <30 kg

AKI, acute kidney injury; APACHE, Acute Physiology and Chronic Health Evaluation; CRRT, continuous renal replacement therapy; CVVHDF, continuous veno-venous hemodiafiltration; CVVH, continuous veno-venous hemofiltration; CVVHDF, continuous veno-venous hemodialysis; GRADE, Grading of Recommendations, Assessment, Development and Evaluation; IL, interleukin; KDIGO, Kidney Disease: Improving Global Outcomes; MAP, mean arterial pressure; NA, not applicable; PaO₂/FiO₂, partial pressure-to-fractional inspired oxygen ratio; PCT, procalcitonin; PP, practice point; R, recommendation; RCT, randomized clinical trial; SCUF, slow continuous ultrafiltration; SOFA, Sequential Organ Failure Assessment; HIT, heparin-induced thrombocytopenia.

Treatment algorithm for oXiris filter use in patients needing CRRT with sepsis/septic shock, severe COVID-19 or other hyperinflammatory states. AKI, acute kidney injury; APACHE, Acute Physiology and Chronic Health Evaluation; CRP, C-reactive protein; CRRT, continuous renal replacement therapy; CVVH, continuous veno-venous hemofiltration; CVVHD, continuous veno-venous hemodialysis; CVVHDF, continuous veno-venous hemodiafiltration; EAA, endotoxin activity assay; ECMO, extracorporeal membrane oxygenation; HIT, heparin-induced thrombocytopenia; SOFA, Sequential Organ Failure Assessment; KDIGO, Kidney Disease: Improving Global Outcomes; PCT, procalcitonin; IL, interleukin; PaO₂/FiO₂, partial pressure-to-fractional inspired oxygen ratio; SCUF, slow continuous ultrafiltration; TNF, tumor necrosis factor.

Statement 1.1. We suggest using oXiris filters in sepsis or septic shock patients requiring CRRT with hemodynamic instability, hyperinflammatory state, severe lactic acidosis, or coagulation dysfunction (Recommendation; GRADE level: Low (++) ; Consensus level: 92.9%)

Key evidence for this statement includes two RCTs. A pilot RCT enrolling 16 patients with surgical septic shock due to Gram-negative infection and AKI reported that oXiris filters may improve hemodynamic status during continuous renal replacement therapy (CRRT) when compared to an AN69ST filter, based on reduced norepinephrine (NE) dose in the oXiris filter group (reduction of 0.11 µg/kg/min at 8 h, $p = 0.017$) [19]. Septic shock in this study was defined as the need for vasoactive therapy to maintain mean arterial pressure (MAP) ≥ 65 mm Hg and lactate elevation to >2 mmol/L despite adequate volume resuscitation [19]. A randomized crossover study was conducted on 16 patients with septic shock associated with AKI who had endotoxin levels >0.03 EU/mL [18]. Patients were enrolled to treatment with the oXiris filter or a standard filter [18]. Compared to patients in the standard filter group, those in the oXiris filter group had reduced endotoxin levels ($p = 0.05$ at 16 h) and reductions in tumor necrosis factor (TNF)- α , interleukin (IL)-6, and IL-8 levels ($p = 0.008$, all three) [18].

Observational studies have also shown beneficial outcomes associated with oXiris filters in critically ill septic patients. A retrospective study of 10 critically ill septic patients treated with the oXiris filter within 3 h of fluid resuscitation reported a 36% reduction in vasopressor use within 12 h and a 38% change in MAP over 72 h [42]. A single-center retrospective cohort compared 30 patients with septic shock ($n = 30$) to 46 patients treated with an AN69 filter. Patients in the oXiris filter group had lower 28-day mortality than those in the control group (73.3% vs. 47.3%, respectively [$p < 0.001$]) and reductions in lactate and NE dosages compared with controls [51].

However, there remain some uncertainties surrounding the benefits of the oXiris filter in septic patients. In the ENDoX trial, an RCT that enrolled patients with severe refractory septic shock with high levels of endotoxemia and at least single organ failure, patients were randomized to one of hemoadsorption (toraymyxin), adsorption hemofiltration (oXiris filter), or standard of care ($n = 10$ patients each arm) [23]. Neither intervention showed a reduction in endotoxin activity or cytokine levels compared with the standard of care [23]. A meta-analysis of 14 studies ($n = 304$ treated with oXiris filters) showed that although the use of the oXiris filter was associated with benefits in 28-, 7-, and 14-day mortalities and length of ICU stay compared with other filters, 90-day mortality, ICU and hospital mortality, and length of hospital stay were comparable [15].

Sepsis and AKI patients frequently have coagulation abnormalities, and there is a correlation between sepsis severity and thrombocytopenia [103]. The grafted heparin layer of the oXiris filter

may reduce thrombogenicity [104], and a real-world study of oXiris filter use in patients with septic shock requiring renal support reported that only 2 of 35 patients needed coagulation [58].

Statement 1.1 may be of particular importance for patients with contraindications to heparin (platelet count $\leq 50 \times 10^9 /L$) and regional citrate anticoagulation (RCA) (lactate ≥ 4 mmol/L) due to coagulation dysfunction, severe lactic acidosis, or other reasons. This recommendation is aligned with a 2021 consensus publication based on European clinical experience with oXiris filters [12]. Cut-off levels for biomarkers associated with septic shock vary between studies and are discussed in more detail in Statement 3.1.

During the formulation of this statement, there was discussion among the experts on whether the patients' requirement for CRRT should be included or not. While there are some data showing a benefit of oXiris filters in patients without, but at risk of, AKI, such as the SIRAKI02 study [17] discussed below, evidence in this population is limited, and the evidence for oXiris filters is predominantly from studies of patients requiring CRRT.

Statement 2.1 We suggest the use of oXiris filters in patients with severe COVID-19 requiring CRRT (PP; Consensus level: 85.7%)

Several studies have reported beneficial effects of using oXiris filter in patients with severe COVID-19 infection. A prospective cohort analysis of 44 critically ill COVID-19 patients treated with oXiris filters reported statistically significant reductions in biomarkers of cytokine storm, including C-reactive protein (CRP) and procalcitonin (PCT) and improved IL-6 control [36]. Another prospective observational study of 15 oXiris filter-treated ICU patients with COVID-19 (and 19 control patients) reported significant reductions of Sequential Organ Failure Assessment (SOFA) scores, improved respiratory status, and better X-ray severity scores after 72 h of treatment, whereas control patients showed deterioration [37]. Another prospective study of 37 ICU patients with COVID-19 reported a significant decrease in IL-6 levels and improvement of SOFA scores within 48 h (median decrease from 13 to 8, $p = 0.001$) [29]. While a retrospective multicenter study comparing 35 oXiris filter CRRT patients to 23 standard CRRT patients found that 31.4% of oXiris filter patients were alive and ventilator-free at 30 days versus 4.3% in the control group (adjusted OR 5.97, $p = 0.117$) [57]. Levels of IL-6 and partial pressure-to-fractional inspired oxygen (PaO_2 / FiO_2) ratios also improved significantly at 24 and 72 h [57]. Another retrospective cohort study comparing 25 oXiris filter-treated COVID-19 patients with AKI to 60 standard filter patients found fewer ventilator and ICU days in the oXiris filter group, though mortality and dialysis dependence at discharge were similar between groups [56]. Overall, these studies indicate that early oXiris filter initiation in severe COVID-19 cases may help mitigate cytokine storms and prevent multi-organ failure.

A case study of 6 patients with severe COVID-19 pneumonia treated with endotoxin adsorption included 1 patient treated with the oXiris filter for 72 h. IL-6 concentrations declined during CRRT with the oXiris filter; the patient developed AKI and subsequently recovered. All patients survived and were free from ventilation [55]. In a single case study of a mechanically ventilated COVID-19 patient with AKI, oXiris filter use was associated with reduction in IL-6, from 34.5 to 8.6 pg/mL (pre- to post-therapy) and gradual improvement of the patient, including complete recovery of kidney function [13]. The authors of this case report also proposed a treatment algorithm for use of oXiris filter in severe COVID-19 patients [13]. Overall, these studies show the efficacy of early initiation of oXiris filter treatment in severely ill COVID-19 patients to prevent cytokine storm and multi-organ failure.

Statement 2.2. We may consider the use of oXiris filters in patients with hyperinflammatory states requiring CRRT (PP; consensus level: 92.9%)

By reducing cytokine and endotoxin levels, the oXiris filter is potentially beneficial for hemodynamic stability in patients with conditions including severe burns, severe tropical infections, and severe

pancreatitis. Key supporting evidence for Statement 2.2 was compiled from five case reports/series [59 , 72 , 105 , 106]. A case series of 5 patients with severe burns and with sepsis and AKI evaluated changes before and 24 h after treatment with oXiris filters. Improvements were observed, including increased urine volume ($p = 0.039$) and decreased SOFA scores ($p < 0.001$), with significant changes in platelet count ($p = 0.001$) and serum sodium levels ($p = 0.016$) [106]. Three case reports or case series in patients with severe acute pancreatitis, acute necrotizing pancreatitis leading to acute liver ischemia and decompensated hepatic failure, and post-cardiac surgery AKI also showed that the use of oXiris filters was associated with reduced levels of inflammatory mediators [59 , 105 , 107].

An example of oXiris filter use in acute respiratory distress syndrome other than COVID-19 is a case report of a post-caesarean section patient with severe tuberculosis and septic shock treated with oXiris filters for 24 h [89]. Compared with pretreatment levels, cytokine concentrations were greatly reduced (IL-6, from 14.42 to 7.84 pg/mL post-therapy) as were levels of inflammatory mediators (TNF- α , from 76.16 to 20.04 pg/mL post-therapy). Posttreatment, this patient improved and was able to breathe without ventilation 3 days after presentation [89].

Other examples of successful use of the oXiris filter in patients with severe infection include a case report of a 12-year old girl with severe dengue and multiple organ failure, for whom the oXiris filter was combined with extracorporeal liver support using an HA330 hemoadsorption cartridge [108]. A 15-year old patient with severe leptospirosis with multi-organ involvement and septic shock was treated with the oXiris filter for metabolic acidosis and cytokine adsorption for 35 h [109]. Rapid decrease in vasopressor requirements, and lactate and PCT levels were reported, and the patient was discharged from the ICU after 7 days [109]. This is a PP rather than a recommendation due to the limited evidence base, which is predominantly small case series and single case reports.

Statement 2.3: We recommend that the use of the oXiris filter could be considered as a potential kidney-protective intervention in cardiac surgery patients during cardiopulmonary bypass (recommendation: GRADE level – moderate [+++]; consensus level: 92.9%)

Cardiac surgery-associated (CSA)-AKI is caused by multiple mechanisms, including hypovolemia, exposure to nephrotoxic drugs, and exposure to the cardiopulmonary bypass (CPB) circuit, and has an incidence of up to 40% [17 , 110]. In the double-blind, two-center SIRAKI02 study, 343 patients at high risk of CSA-AKI undergoing CPB for cardiac surgeries, including coronary artery bypass grafting and valvular heart surgeries, were randomized to receive CPB with the oXiris filter in the slow continuous ultrafiltration (SCUF) modality ($n = 169$) or to CPB with usual care ($n = 174$) [17]. The primary outcome, the rate of CSA-AKI 7 days after randomization, was 28.4% (95% CI, 21.7%–35.8%) in the oXiris filter group vs. 39.7% (95% CI, 32.3%–47.3%) in the standard care group ($p = 0.03$). No clinically significant differences were seen in secondary outcomes (ICU stay, hospital stay, 7-, 28-, or 90-day survival), but significant reductions in TNF- α and IL-8 plasma concentration during the surgical procedure were found in the oXiris filter vs. standard care group ($p < 0.05$) [1]. A case study has also shown beneficial effects of the oXiris filter in a patient with CSA-AKI and septic shock [107].

Statement 3.1. We may consider the initiation of oXiris filter treatment in patients with the following clinical and biomarker criteria (PP; consensus level: 100%)

Hemodynamic instability with high-dose vasopressors (NE >0.5 $\mu\text{g/kg/min}$) or more than 2 vasopressors used after adequate fluid management

Sepsis-associated AKI mandating CRRT initiation

Persistent elevation of lactate levels, Acute Physiology and Chronic Health Evaluation (APACHE) or SOFA score.

Primary markers: Elevated endotoxin levels

Increased commonly used inflammatory markers (white cell count, CRP, PCT)

Other markers of interest: Elevated cytokines (IL-6, IL-10, TNF- α).

Statement 3.2. oXiris filter treatment should be initiated as soon as possible after determination of initiation criteria (PP; consensus level: 100%)

The suggested clinical and biomarker criteria to guide oXiris filter initiation are summarized in Table 1. Based on analyses of 7 studies of patients with sepsis and/or sepsis-associated AKI (one RCT, two observational studies, four case series/studies), hemodynamic instability was the most frequent criterion to initiate CRRT with the oXiris filter in patients with sepsis and/or sepsis-associated AKI [18 , 41 , 48 , 75 , 79 , 86]. The median time from ICU admission to oXiris filter initiation is generally 20–25 h [28 , 61]. A single-center case series has compared outcomes in initiating the oXiris filter <24 h or $\geq$ 24 h after ICU admission in septic shock patients needing kidney support [58]. Although there was no statistically significant difference in mortality between groups, significant reductions in NE dose, inotropic score, vasopressor dependency index, and platelet count over the course of treatment were only reported in the <24-h subgroup [58].

The current literature reports that the initiation of treatment with the oXiris filter for patients experiencing hemodynamic instability due to sepsis or septic shock is guided by a combination of clinical assessments and specific biomarkers [15 , 18 , 19 , 23 , 41 , 80]. Other parameters used to guide oXiris filter initiation include lactate levels [22] and SOFA scores [49], and studies have demonstrated use of the APACHE II scores to monitor treatment effect [37 , 80].

Overall, expert opinion was that the early use of the oXiris filter could be indicated in septic patients with renal failure and high catecholamine requirements, hemodynamic instability, or hemodynamic incoherence with poor perfusion due to impaired microcirculation. Elevated levels of inflammation-associated biomarkers such as IL-6 and PCT, and evidence of endotoxemia, can also guide early intervention. The former may be particularly appropriate – a systematic review reported that treatment with the oXiris filter is associated with significantly lower levels of IL-6 compared with other filters [15]. Although RCTs have demonstrated the use of endotoxin threshold levels to guide oXiris filter initiation and the use of changes in cytokine levels to evaluate its effect [18 , 23], cut-off levels vary among studies. Therefore, specific cut-off levels have not been proposed. Endotoxin assays, namely, the endotoxin activity assay (EAA) and limulus amoebocyte lysate assay, are rarely used in routine clinical practice in APAC. Furthermore, interpretation of endotoxin levels and their implications for treatment are hampered by variability between different testing methods and inconsistent associations between plasma endotoxin levels and other inflammatory markers or metabolic changes [111 , 112]. In settings where EAA is unavailable, elevated PCT may be an informative surrogate biomarker for suspected endotoxemia, based on its moderate correlation with endotoxin levels in Gram-negative sepsis [113 , 114]. However, studies of the diagnostic accuracy of PCT for sepsis have shown variable results, and PCT levels are affected by renal function and may be elevated by noninfectious disorders [114]. As such, the correlation between PCT and endotoxin levels requires further validation in diverse populations [114]. Due to the limited evidence supporting these criteria, both biomarkers and clinical criteria must guide the decision to initiate the oXiris filter, and this decision must be individualized based on the clinical judgment of the prescribing physician. Due to the limited evidence supporting these criteria, both biomarkers and clinical criteria should be used to guide the decision to initiate the oXiris filter, and this decision must be individualized based on the clinical judgment of the prescribing physician.

Statement 4.1. We suggest evaluating the effectiveness of the oXiris filter based on the improvement of hemodynamic parameters, lactate level, and SOFA score within the first 72 h of initiation (PP; consensus level: 100%)

Using the oXiris filter may improve hemodynamic status during initial CRRT in severe surgical septic shock with AKI, and vasopressor dose, typically NE, is a commonly used primary endpoint to monitor hemodynamic improvement in studies of oXiris filter use [19 , 21 , 45 , 46]. A randomized study compared treatment with the oXiris filter or an AN69ST filter in patients with septic shock and AKI [19]. In the oXiris filter group, the NE infusion rate was decreased by 0.06, 0.05, and 0.11 $\mu\text{g/kg/min}$ at 4 h ($p = 0.005$), 6 h ($p = 0.038$), and 8 h ($p = 0.017$) of CRRT treatment, respectively, compared to the AN69ST group [19]. Lactate levels and SOFA scores are also appropriate parameters for monitoring. In a meta-analysis of 14 publications (4 RCTs and 10 cohort studies) involving 304 adult patients with sepsis treated with the oXiris filter, treatment with the oXiris filter during CRRT was associated with lower 7-, 14-, and 28-day mortalities (OR: 0.42, 0.42, 0.53, respectively), reduced lactate levels ($p = 0.001$), improved SOFA scores ($p < 0.00001$), and reduced NE doses ($p < 0.0001$), compared to other filters [15]. Hemodynamic control can usually be achieved within 72 h, and this time point has previously been noted in a previous consensus publication on oXiris filter use in septic shock patients [12]. Therefore, monitoring should begin immediately after initiation and continue throughout the 72-h window.

Statement 4.2. A reduction in the levels of potential inflammatory biomarkers within 72 h may be considered as an effective measure of oXiris filter efficacy, based on resource availability (PP; consensus level: 100%)

The analysis of inflammatory biomarkers (e.g., IL-6, PCT) and endotoxin levels during oXiris filter treatment is supported by an RCT showing significant reductions in PCT and IL-6 levels after the first treatment compared to pre-CRRT levels in the oXiris filter group versus comparator (AN69ST filter) [19]. In the oXiris filter group, median PCT levels decreased from 52.79 (interquartile range [IQR] 9.03, 100.00) to 23.46 (IQR, 4.18, 84.90) $\mu\text{g/L}$ ($p = 0.046$ pre- vs. posttreatment) during the first CRRT treatment (median duration 23.5 h) [19]. Significant decreases in median IL-6 levels from 10,457.17 (IQR, 8,150.00, 15,528.87) to 3,080.15 (IQR, 527.62, 9,806.61) pg/mL were also seen in the oXiris filter group (pre- vs. posttreatment, respectively; $p = 0.043$) [19]. Improvements in IL-6 associated with oXiris filter treatment have also been reported in a meta-analysis of five studies [15], and reductions in endotoxin, IL-6, and PCT levels associated with oXiris filter use have also been reported in numerous prospective and retrospective real-world studies [32 , 36 , 46 , 49 , 57 , 73 , 89 , 90]. The consistent results across different study types and patient populations suggest endotoxin levels and inflammatory biomarkers such as IL-6 and PCT as appropriate measures of a patient's inflammatory status and can be used to monitor oXiris filter treatment.

Statement 5.1. Treatment with the oXiris filter can be discontinued because of treatment success or futility (PP; consensus level: 100%)

Treatment success criteria: Improvement in hemodynamic parameters with a reduction of vasoactive therapy ($\geq 50\%$ reduction) as early as 24 h

Improvement in clinical parameters (MAP/heart rate/ $\text{PaO}_2/\text{FiO}_2$ ratio) after 24 h

Reduction in inflammatory biomarkers: lactate/CRP/PCT/IL-6 within 24 h.

Treatment futility criteria: No improvement in hemodynamic parameters/dependence on vasopressors after 72 h.

Based on studies, including an RCT, three case series, a cohort study, and an observational study [19 , 49 , 58 , 61 , 90 , 93], treatment success can be defined by improvement in hemodynamic parameters with a reduction of vasoactive therapy ($\geq 50\%$ reduction) as early as 24 h (summarized in Table 1). Other definitions of success include reductions in lactate, PCT, or IL-6 levels after 24 h, or improvement in urine output. Treatment futility is defined as the absence of improvement in hemodynamic parameters or dependency on vasopressors after 72 h.

Statement 6.1. We may consider changing the oXiris filter at 12 to 24 h to maximize the adsorptive capacity, if beneficial (PP; consensus level: 100%)

The capacity of the oXiris filter to adsorb cytokines and endotoxin diminishes over time due to saturation effects [104], and the instructions for use recommend filter changes every 24 h [115]. In two small randomized studies of critically ill patients with AKI or end-stage kidney disease receiving CRRT, the oXiris filter had a median life span (defined by forced disconnection due to filter clotting or excessively high or low transmembrane pressure) of 13–16 h [22 , 24]. A retrospective observational study of septic shock patients with AKI treated with oXiris filters reported a median of 3.5 filters used over a CRRT duration of 48 h [49].

In case reports involving patients with septic shock post-liver transplant, gastrointestinal septic shock with AKI, and septic shock with underlying liver malignancy, filter changes were implemented every 12 to 24 h [87 , 88 , 116], and one case report of a patient with concomitant COVID-19 and bacterial infections reported a total of 4 filter changes within a 30-h period [75]. Shorter intervals between filter changes may maximize adsorption capacity [87 , 88], which may be of particular benefit in complex cases with high inflammatory burden.

In a study of sepsis or septic shock patients undergoing CRRT using non-fractionated heparin, filters were typically changed after clotting or at 24-h intervals [30]. Expert opinion is that changing the filter every 12–24 h is likely to maximize adsorptive capacity.

Statement 6.2. We may consider prolonging the use of the oXiris filter to 72 h as kidney support, particularly if the patient shows signs of stabilization or improvement (PP; consensus level: 100%)

Several studies demonstrated the feasibility of prolonging the oXiris filter lifespan for the sole purpose of kidney support. An overall median filter lifespan of 23 h was reported in a case series of patients with septic shock, but 20% of patients had a median filter lifespan of ≥ 48 h [58]. In a case series of sepsis-induced AKI ($n = 6$), the mean filter life was extended to 61 h using a citrate anticoagulation-based continuous veno-venous hemofiltration (CVVH) regimen [28]. The feasibility of prolonging the filter changeover interval to 72 h has been demonstrated in a retrospective study of patients with hematological malignancy and septic shock [50]. The manufacturer's instructions for use specify a maximum duration of 72 h due to the risk of rupturing of pump segments [115]. In summary, these studies suggest that prolonging the filter use to 72 h is feasible, particularly when patients are showing signs of improvement. The decision to prolong changeover time should be guided by the treating team's clinical judgment.

Statement 7.1. We suggest the use of continuous veno-venous hemodiafiltration, CVVH, continuous veno-venous hemodialysis, or SCUF as the modality of oXiris filter treatment (PP; consensus level: 85.7%)

The oXiris filter is designed for use in four veno-venous therapies: continuous veno-venous hemodiafiltration (CVVHDF), CVVH, continuous veno-venous hemodialysis, and SCUF [115]. Supporting evidence is derived from an analysis of 17 publications, including two randomized crossover studies, two prospective observational studies, six retrospective cohort studies, and seven case reports, encompassing a total of 382 patients [13 , 24 , 41 , 45 , 50 , 51 , 57 , 61 , 75 , 80 , 84 , 86 – 89 , 91 , 102]. Data on the modality used with oXiris filters were available for 374 patients, of whom 222 (59.4%) were treated with CVVHDF and 145 (38.8%) were treated with CVVH [13 , 24 , 41 , 45 , 50 , 51 , 57 , 61 , 75 , 80 , 84 , 86 – 89 , 91 , 102]. The SCUF modality can be applied during CPB by adding a filter to the bypass circuit, as demonstrated in the SIRAKI02 trial, with the goal of achieving the adsorption of pro-inflammatory molecules. Despite the predominance of CVVHDF followed by CVVH as the main modalities used, there are currently no studies directly comparing the different modalities of oXiris filters in terms of outcomes such as mortality or reduction of inflammatory biomarkers. Therefore, the choice of modality should be guided by patient-specific factors and judgment of the physician.

Statement 7.2. We suggest using 20–25 mL/kg/h as the delivered dose of oXiris filter treatment (recommendation; GRADE level: very low [+]; consensus level: 100%)

The relationship between effluent dosage and the cytokine adsorption capacity of the oXiris filter is currently unknown. The effluent dosage in oXiris filters primarily reflects its function in small solute clearance and should follow standard CRRT guidelines [117]. An initially higher effluent dosage may be necessary for severe metabolic derangements such as hyperkalemia or severe metabolic acidemia. The prescribed dose of oXiris filters is typically 20–30 mL/kg/h, and blood flow settings are usually 150–200 mL/min in the studies evaluated [24 , 41 , 45 , 51 , 61]. However, dose may be affected by catheter function and anticoagulation use. In a study using citrate anticoagulation, blood flow rates were generally around 150 mL/min or lower [41]. As with conventional CRRT filters, higher blood flow can decrease the filtration fraction during hemofiltration, diminish the risk of clotting [118], and thereby reduce treatment interruption.

Statement 7.3. We suggest applying individualized anticoagulation strategies recommended by the 2012 KDIGO AKI guidelines (PP; consensus level: 100%)

Membrane clotting is a significant complication that can potentially reduce the clinical effectiveness of CRRT, including oXiris filter sets [24 , 119]. In an RCT assessing anticoagulation-free treatment with oXiris filter (in comparison with an M150 filter), the average filter life was 13 h [24]. Data comparing anticoagulation strategies with the oXiris filter are scarce, but one example is a prospective observational study from the oXiris NET Registry Working Group that included data from 97 patients, 19 (18.6%) of whom developed clotting [41]. A regression analysis identified hematocrit, serum PCT level, and anticoagulation strategy as independent predictors of clotting [41]. Both heparin and RCA were protective compared to no anticoagulation, with no significant difference in filter lifespan between the two anticoagulation methods [41]. Data from 15 publications, including 337 patients (3 prospective observational studies, 5 retrospective cohort studies, and 6 case reports) [13 , 34 , 45 , 50 , 51 , 57 , 61 , 75 , 80 , 84 , 87 – 89 , 91 , 102], showed that 174 patients (56.1%) were treated with RCA, 79 patients (25.5%) received heparin, while 84 patients (18.4%) received no anticoagulation.

Based on the Kidney Disease: Improving Global Outcomes (KDIGO) 2012 clinical practice guideline for AKI patients treated with CRRT, RCA is preferred to heparin for reducing systemic bleeding while maintaining circuit anticoagulation, unless contraindications like high lactate levels or severe liver failure are present [117 , 120]. As sodium citrate acts by forming a complex with ionized calcium, patients receiving citrate anticoagulation should undergo intensive metabolic monitoring, including acid-base status, sodium, and total and ionized calcium levels [117]. Heparin is also effective and widely used but is associated with a higher risk of systemic bleeding [117 , 121]. The use of anticoagulation minimizes filter clotting and treatment interruption. The choice of anticoagulation should be tailored to the patient's condition, contraindications, and institutional experience.

Statement 7.4. The oXiris filter can be combined with other extracorporeal life support therapies (PP; consensus level: 100%)

Evidence from both prospective and retrospective case series supports the safe use of the oXiris filter combined with extracorporeal membrane oxygenation (ECMO) for multi-organ support in critically ill patients with severe COVID-19. A prospective case series of 8 patients with severe COVID-19 treated with ECMO and the oXiris filter reported significant improvement in hemodynamic stability and initial renal recovery [34]. A retrospective case series of 5 patients with severe COVID-19 treated with oXiris filters included 2 patients who also received ECMO [80]. Compared with pretreatment, both patients experienced decreases in inflammatory biomarkers, SOFA, and APACHE II scores, and both patients had increases in PaO₂/FiO₂ [80]. Expert opinion is that additional anticoagulation for the oXiris filter may not be needed in patients receiving systemic anticoagulation for ECMO.

Statement 8.1. The oXiris filter should not be used in the following conditions: Pediatric patients with body weight <30 kg

Patients with heparin-induced thrombocytopenia (PP; consensus level 100%)

The use of the oXiris filter in managing pediatric septic shock has been demonstrated [47 , 91], but cautious use is emphasized due to the small blood volume in children under 30 kg [47], and the instructions for use restrict oXiris filter to patients ≥ 30 kg [115]. The oXiris filter includes a heparin-grafted membrane to reduce local thrombosis [104 , 115]. Therefore, the oXiris filter is contraindicated in patients with contraindications to heparin, such as those with heparin allergy or type II thrombocytopenia caused by heparin [115].

Statement 9.1. Antibiotic adsorption by the oXiris filter should be considered during oXiris filter treatment (PP; consensus level: 100%)

In vitro studies show that adsorption of vancomycin and amikacin by polyacrylonitrile filters is dependent on the filter material and is not reversed even when circulating concentrations decrease [122 , 123]. A pharmacokinetic model based on plasma samples from sepsis patients treated with the oXiris filter suggested that clearance of meropenem with the oXiris filter may be increased compared with other CRRT filters, and doses higher than those used in standard dosing regimens may be needed to ensure minimum inhibitory concentrations are reached in critically ill patients [39 , 124]. Altogether, these data suggest that monitoring must be conducted to ensure appropriate drug concentrations are maintained during oXiris filter treatment [104]. Further research into this topic is needed.

Multiple opportunities for future research were identified during the formulation of these statements (Table 2). For several of the topics described above, evidence is limited to case studies or small case series. There is a need to conduct well-designed RCTs to identify the efficacy of the oXiris filter for short- and long-term outcomes in different populations. The heterogenous nature of patients with sepsis and hyperinflammatory conditions is also a challenge [14]. In RCTs and other prospective studies, heterogeneity could be reduced through specific inclusion criteria. The assessment of clinically relevant endpoints, including hemodynamic and organ improvement, as well as ICU stay rather than only mortality, should be performed [125 , 126]. The potential benefit of a more selective approach is exemplified by the EUPHRATES trial which examined the impact of polymyxin B hemoadsorption on mortality in patients with septic shock and endotoxemia, defined as $EAA \geq 0.60$ [127]. In the initial study, no difference was found in 28-day all-cause mortality [127]. However, in some of the study population, the burden of endotoxin activity was extreme ($EAA \geq 0.9$) [127]. In a post hoc analysis of patients with EAA between 0.6 and 0.89, measurable responses in MAP, ventilator-free days, and mortality were seen [127], implying that the use of EAA in patient selection may have allowed treatment to be focused on individuals with the highest potential benefit. The results of EUPHRATES also highlight the importance of measuring endotoxin levels in patients undergoing EBP; better methods of monitoring endotoxin levels may be needed.

Future research priorities for clinical use of the oXiris filter

Because enrolling a large population of homogenous sepsis patients with AKI into a randomized study is a challenging proposition, patient registries will also have an important role in identifying those who are more likely to benefit from treatment [128]; the oXiris Net registry is a notable example [70]. There is a need to develop efficacy endpoints for EBP studies other than mortality, which is highly variable across centers, sepsis, and AKI phenotypes [126]. Furthermore, mortality cannot be considered as a patient-centered endpoint [125].

Another unmet need is for biomarkers or risk prediction tools to identify patients most likely to benefit from EBP with the oXiris filter. A post hoc analysis of two large studies suggested that septic patients with high endotoxin levels having abnormal coagulopathy and high lactate levels may

benefit most from polymyxin B hemoadsorption [129]. A propensity score matching analysis of a large database found significantly lower mortality in patients receiving polymyxin B hemoadsorption who had medium SOFA scores on admission (7–12) versus those with higher scores [130]. This suggests that hemoadsorption therapy may be beneficial in moderate but not severely ill patients.

There is a need to establish the optimum duration of the treatment cycle and the number of sessions. It is plausible that patients with higher endotoxin or cytokine levels may require more sessions [131]. The higher cost of the oXiris filter relative to other filters, and the availability of endotoxin testing, may limit access to it, especially in the lower income regions of APAC [11]. Better data on the optimal treatment duration and number of sessions, and analyses of the cost-effectiveness of oXiris relative to other treatment options may reduce this barrier to access. Finally, very limited data are available on the effect of the oXiris filter on circulating levels of antibiotics. Additional data on these impacts, optimized dosing strategies to counteract them, and data on the effects of the oXiris filter on other drug classes are needed.

We have summarized our experience with, and published evidence for, the use of the oXiris filter in patients with sepsis/septic shock and hyperinflammatory states. The recommendations herein are general in nature and should always be personalized to each patient according to the treating team's clinical judgment. EBP with the oXiris filter is still a new and emerging modality, and well-designed RCTs and other studies are needed to further establish its impact on outcomes and role in critical care.

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