Adsorptive hemofiltration for sepsis management: expert recommendations based on the Asia Pacific experience

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To the Editor: In sepsis, bacterial endotoxins play a central role by inducing a dysregulated and exaggerated release of inflammatory mediators and cytokines, often described as the "cytokine storm" or "cytokinemia."[1] Both endotoxins and cytokines have been implicated in the development of organ dysfunction, including acute kidney injury (AKI).[2] Removing circulating endotoxins and excess cytokines from the circulation restores chemotactic gradients, localizing the immune response to the principal site of infection and re-establishing a regulated immune response.[1,3] Therefore, using hemofilters with enhanced endotoxin and cytokine adsorptive properties may bring about additional therapeutic benefits compared with conventional continuous renal replacement therapy (CRRT) filters.

Oxiris is the only CRRT filter capable of simultaneously adsorbing endotoxins and inflammatory mediators while providing renal support.[4,5] Use of Oxiris in the Asia Pacific (APAC) region is increasing and approaching that of Europe in recent years. Existing recommendations for the clinical application of Oxiris are based solely on clinical experience in Europe, and they neither address the role of measuring endotoxin and cytokine levels nor advise on suitable dialysis modalities or frequency of filter changes.[6] Given the diverse socioeconomic and practice environment in APAC,[7] recommendations on the use of Oxiris based on clinical experience in this region are urgently needed.

To meet this need, 14 critical care experts from APAC developed a list of consensus recommendations for Oxiris use in sepsis [Table 1] using a standardized, three-step, modified Delphi-based process. The criteria and administration parameters described provide clinicians with a better understanding of how Oxiris is currently used in expert centers across APAC. At the institutional level, these recommendations guide patient selection and dosage

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Table 1: Summary of key consensus recommendations for CRRT with Oxiris.

Patient population/syndromes	Primarily for patients in critical condition with both septic shock and AKI requiring CRRT • CRRT with Oxiris may also be considered in patients with sepsis or septic shock before KDIGO stage 2 AKI criteria are met, based on clinical indicators that include marked disturbances in hemodynamic stability, microcirculatory function, and organ function • Clinical judgment based on a combination of clinical and laboratory parameters should ultimately drive the decision of whether CRRT with Oxiris is necessary
Clinical criteria for initiation	Marked disturbances in: • Hemodynamic stability (eg, fluid balance, MAP, vasopressor dose); • Microcirculatory function (eg, PCO_2 gap); and/or • Organ function (eg, high SOFA score)
Laboratory criteria for initiation	Indicators of: • Infection severity (eg, elevated levels of PCT, IL-6); • Sepsis severity (eg, lactate levels); • Kidney function (eg, urine output); and/or • Metabolic function (eg, life-threatening electrolyte imbalances)
Initiation timing	Therapy should be initiated as soon as possible upon determining that CRRT with Oxiris is indicated
Frequency of filter change	• Consider changing the filter at 12 to 24 h, especially if cytokine levels remain high (ie, cytokine storm) • Frequency can be augmented if high cytokine levels persist, high filter transmembrane pressure is observed, or imminent circuit clotting is anticipated • Filter change may be extended to 72 h if the patient is improving steadily or during the CRRT discontinuation stage, but clinical judgment should be used
Indicators of treatment success and discontinuation	Evaluated based on a combination of clinical and biological improvements within the first 24 h of Oxiris initiation: • Clinical: Hemodynamic stability and organ function • Biological: Measures of immune response improvement, microbial clearance, and metabolic function
Special populations	Take extra caution when considering Oxiris for the following populations: • Patients with compromised/exhausted vascular access points • Pediatric patients with body weight <30 kg • Patients on palliative care
Contraindications	Patients with heparin-induced thrombocytopenia

AKI: Acute kidney injury; CRRT: Continuous renal replacement therapy; IL-6: Interleukin-6; KDIGO: Kidney Disease Improving Global Outcomes; MAP: Mean arterial pressure; PCO_2: Partial pressure of carbon dioxide; PCT: Procalcitonin; SOFA: Sequential Organ Failure Assessment.

instructions for the use of Oxiris, providing a basis for forming a streamlined management protocol.

Initiating CRRT with Oxiris is recommended when both AKI and septic shock are present. However, in the absence of septic shock, Oxiris may be considered in patients with sepsis before AKI stage 2 criteria are met, based on several key clinical factors such as marked disturbances in hemodynamic stability, microcirculatory function, and organ function.

In the absence of a single specific biomarker to guide CRRT initiation decisions, a range of laboratory parameters can be used to determine the need for Oxiris, including indicators of infection severity, sepsis severity, kidney function, and metabolic function. Although endotoxin removal is a key reason for initiating CRRT with Oxiris, it may not always be feasible to measure endotoxin level because of limitations around availability and reliability of endotoxin assays. In practice, severity of infection and bacteremia could be assessed with more accessible parameters such as procalcitonin and interleukin-6.

The decision to initiate CRRT with Oxiris should be driven by clinical judgment based on a combination of these clinical and laboratory parameters. Upon determining that CRRT with Oxiris would be beneficial for the patient, therapy should be initiated as soon as possible.

The Oxiris filter should be changed at 12 to 24 h if high cytokine levels persist, high filter transmembrane pressures are observed, or imminent circuit clotting is anticipated. However, filter change may be extended up to 72 h if the patient's overall condition and biomarkers continue to improve.

Other components of the system, such as the connection tubing and access catheters, may become compromised before the filter requires replacement; therefore, the duration of Oxiris use should be determined on a case-by-case basis with close monitoring and clinical judgment.

Treatment success should be evaluated based on a combination of clinical observations and improvements in laboratory markers within the first 24 h of Oxiris initiation. In line with the treatment initiation parameters,

improvements in hemodynamic stability, organ function, and immune response, as well as evidence of microbial clearance and stabilization of metabolic function, indicate treatment success and can direct discontinuation of Oxiris. In terms of measuring treatment success, the relative improvement in each of these parameters is more important than specifically defined values or cut-offs.

Oxiris should be used with caution in patients with compromised/exhausted vascular access points, patients with disseminated intravascular coagulation or low platelet counts, pediatric patients with body weight <30 kg, and those receiving palliative care. The use of Oxiris is contraindicated in patients with heparin-induced thrombocytopenia.

The parameters for administering the Oxiris filter do not differ significantly from those used for CRRT with conventional dialysis filters. Regional citrate or systemic heparin should be used as an anticoagulant for CRRT with Oxiris. Whatever treatment modality is chosen, dosing should target an effluent dose of 20 to 35 mL · kg^{-1} · h^{-1} with a blood flow rate of 150 to 200 mL/min, depending on the patient's hemodynamic stability.

Despite mounting evidence of the benefits of removing endotoxins and inflammatory mediators during CRRT for hemodynamically unstable, critically ill patients,[5] the use of Oxiris in APAC is hindered by the limited availability and reliability of endotoxin tests, restricted access to Oxiris, and some clinicians' perception that conventional CRRT filters are an acceptable compromise.

Most importantly, large clinical studies demonstrating benefits of CRRT with Oxiris are lacking. Randomized controlled trials (RCTs) would provide the most valuable evidence and confidence to instruct Oxiris use. However, it would be challenging to design and generate conclusive results from RCTs given the heterogeneous nature of the patients. To fill this gap and provide large-scale evidence in real-world settings, a registry for APAC on Oxiris to record measures important for informing clinical decisions could be established. In addition to helping clinicians understand the impact of Oxiris better, a regional registry could guide future trial design.

While more practice experience is being gathered, expert recommendations can be an effective way of providing timely guidance. The details of the consensus recommendations can be found in the Supplementary Material [Supplementary Digital Content, Figures 1-3, http://links.lww.com/CM9/A756].

Conflicts of interest

All authors attended the face-to-face meeting as part of the modified Delphi-based consensus-gathering process, funded by Baxter, Inc. Minmin Wang, Jacques Goldstein, and Kai Harenski are employees of Baxter, Inc. and hold Baxter stocks but did not influence the consensus development. Matthew Cove is an active consultant for Medtronic and Baxter and receives consulting fees, travel support, and grants from these companies.

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