oXiris

A single CRRT set with multiple benefits for managing critically ill patients with AKI

Adsorption of inflammatory mediators

Heparin-grafted for reduced thrombogenicity

Supports renal function

Making possible personal.
What is oXiris?

A single-use set for continuous renal replacement therapy

- Part of a dedicated range of products to support continuous renal replacement therapy (CRRT), oXiris is a single-use set comprised of a hollow fiber membrane and tubing lines.\(^1\)
- The oXiris set is designed to be used exclusively with the Prismaflex system, for the provision of CRRT and fluid management in patients with acute kidney injury (AKI), fluid overload, or both.\(^1\)

Designed to provide multiple functionalities in a single set

- The oXiris membrane is characterized by three features:\(^1-3\)
  - Permanent heparin graft on the inner membrane surface\(^1,2\)
  - Polyethylenelmine surface treatment\(^1-3\)
  - AN 69 membrane technology – a copolymer of acrylonitrile and sodium methallyl sulfonate\(^2\)

- The features of the oXiris set are designed to **combine three functionalities in a single device**, with multiple potential benefits for managing critically ill patients with AKI.\(^1-8\)

The oXiris membrane is permanently heparin grafted and is designed to have capacity for the adsorption of endotoxin in addition to cytokines.
Managing critically ill patients with AKI requiring CRRT – what potential benefits does the oXiris set offer?

A single set for all CRRT modalities using the familiar Prismaflex system

The oXiris set – three functionalities in a single device:

- Renal function support via a choice of CRRT modalities
- Capacity to remove cytokines and endotoxin without the need for additional equipment
- Support CRRT efficiency by offering clinically acceptable filter life when used with anticoagulation therapy, with potential to minimize treatment interruptions and reduce workload for care providers.
Elevated levels of specific inflammatory mediators may be associated with poor outcomes in patients with AKI

• Critically ill patients are a heterogenous population likely to require multiple therapeutic interventions\(^1\) – a characteristic that complicates assessment of treatment outcomes in the AKI setting.

• Consequently, confirmation of an association between removal of inflammatory mediators during CRRT and improved clinical outcomes for patients with AKI, in a randomized controlled trial setting, may be challenging.

• However, some observational studies have found elevated levels of specific cytokines or endotoxin in patients with AKI to be associated with:

  - Increased mortality\(^{11,12}\)
  - Poorer renal recovery\(^{13}\)

Findings from such observational studies suggest that removal of inflammatory mediators is a potential therapeutic target in the management of critically ill patients with AKI.
What evidence is there to support the adsorption of inflammatory mediators by the oXiris membrane?

Findings from in-vitro and observational studies suggest that the oXiris membrane has capacity to adsorb inflammatory mediators from the circulation\textsuperscript{4–7,14}

\textbf{In-vitro} filtration experiments have shown the oXiris membrane to:

- Have capacity to remove spiked endotoxin from the plasma of healthy volunteers\textsuperscript{14}
- Significantly reduce levels of high mobility group box 1 (HMGB1) – a DNA-binding protein involved in activation of the systemic inflammatory response\textsuperscript{a} – from bovine serum by membrane adsorption.\textsuperscript{4}

\textsuperscript{a}Elevated levels of HMGB1 have been observed in patients with AKI.\textsuperscript{15}

Findings from published \textbf{observational studies} suggest that:

- CRRT with the oXiris membrane may reduce plasma levels of specific cytokines in patients with AKI or renal failure, plus sepsis or septic shock\textsuperscript{5,6}
- While the capacity of the oXiris membrane to remove endotoxin has not been demonstrated in patients with AKI, reduced endotoxin activity has been demonstrated in patients with endotoxemia\textsuperscript{b} who required CRRT.\textsuperscript{9}

\textsuperscript{b}The oXiris membrane is indicated for the provision of CRRT and fluid management in patients with renal failure, fluid overload, or both.\textsuperscript{1} Please refer to the product instructions for use for a comprehensive overview of correct usage.

\textbf{Note}: Findings from preclinical, single-arm, and observational studies have not been confirmed in randomized controlled trials. Some data are preliminary and have not been peer reviewed.
Adsorption of inflammatory mediators

In vitro study: Reduced levels of bovine serum HMGB1 with the oXiris membrane

The efficacy of two membranes for the removal of HMGB1 from bovine serum was compared over 120 minutes. After 15 minutes, serum concentration of HMGB1 was significantly reduced with the oXiris membrane but not with a polyarylether sulfone hemofiltration set. Electron microscopy confirmed HMGB1 adsorption on the membrane. *p = statistically significant. HMGB1, high mobility group box 1; PAES, polyarylether sulfone; SD, standard deviation.

Single-arm, observational study: Reduced blood cytokine levels following CRRT with the oXiris membrane in patients with sepsis and renal failure

Adult patients with sepsis/septic shock and renal failure (n = 40) underwent high-volume HDF using the oXiris membrane. After 24 hours of treatment, blood levels of IL-6 and procalcitonin were significantly decreased from baseline. *p < 0.05. HDF, hemodiafiltration; IL, interleukin; SD, standard deviation.

Note: Limited data are available to support the removal of cytokines with the oXiris membrane and available studies lack control groups. The findings of this study are not necessarily in line with all published literature.
Adsorption of inflammatory mediators

Summary of single-arm, observational studies: Significantly reduced levels of IL-6, procalcitonin, and endotoxin following CRRT with the oXiris membrane

<table>
<thead>
<tr>
<th>Study</th>
<th>CRRT modality</th>
<th>Inflammatory mediator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prospective observational pilot study in adults with AKI caused by sepsis or septic shock (n = 34)⁵</td>
<td>oXiris membrane-CVVHDF</td>
<td>✓</td>
</tr>
<tr>
<td>Prospective observational study in patients with renal failure and sepsis/septic shock (n = 40)⁶</td>
<td>oXiris membrane-high volume HDF</td>
<td>✓</td>
</tr>
<tr>
<td>Prospective observational study in adults with septic shock requiring RRT (n = not reported)⁹</td>
<td>oXiris membrane-CRRT</td>
<td>✓</td>
</tr>
</tbody>
</table>

Summary of published observational studies that have reported statistically significant (p < 0.05) reductions in levels of inflammatory mediators following CRRT with the oXiris membrane.
*The oXiris membrane is indicated for the provision of CRRT and fluid management in patients with AKI, fluid overload, or both. Please refer to the product instructions for use for a comprehensive overview of correct usage.

AKI, acute kidney injury; CRRT, continuous renal replacement therapy; CVVHDF, continuous venovenous hemodiafiltration; ET, endotoxin; HDF, hemodiafiltration; IL-6, interleukin-6; PC, procalcitonin; RRT, renal replacement therapy.

• The oXiris membrane has been shown to have capacity for the adsorption of endotoxin and the pro-inflammatory protein, HMGB1, in vitro.⁴,¹⁴

• In some observational studies, CRRT with the oXiris membrane has been reported to:
  – Reduce levels of the pro-inflammatory cytokines, IL-6 and procalcitonin, in patients with AKI or renal failure⁵⁻⁷
  – Reduce endotoxin activity level in patients with endotoxemia who required CRRT.⁹

**Note:** Findings from preclinical, single-arm, and observational studies have not been confirmed in randomized controlled trials. Some data are preliminary and have not been peer reviewed.
Is the removal of inflammatory mediators during CRRT with the oXiris membrane associated with improved clinical outcomes for patients with AKI?

Some observational studies have reported improvements in clinical outcomes following CRRT with the oXiris membrane in patients with AKI. These improvements include reduced levels of circulating inflammatory mediators and observed improvements in organ function and hemodynamic stability.
Potential for improved organ function and hemodynamic stability

Note: Findings from preclinical, single-arm, and observational studies have not been confirmed in randomized controlled trials. Some data are preliminary and have not been peer reviewed.

**Observational study: Improved SOFA scores following CRRT with the oXiris membrane in patients with AKI**

![Graph showing improved SOFA scores](Graph)

Adult patients (n = 6) with AKI due to infection with Gram-negative bacteria underwent CVVH with the oXiris membrane. Clinical outcomes were compared with historic matched controls who had been treated with post-dilutional CVVH using a polysulfone high-flux hemofilter. Organ function, as assessed by SOFA score, was significantly improved at 48 hours post-initiation of treatment in the oXiris membrane group but not in the control group.8

*p = 0.013. AKI, acute kidney injury; CVVH, continuous veno-venous hemofiltration; SOFA, Sequential Organ Failure Assessment.

**Single-arm, observational study: Increased arterial pressure following CRRT with the oXiris membrane in patients with AKI**

![Graph showing increased arterial pressure](Graph)

Adult patients with AKI caused by sepsis or septic shock (n = 34) underwent CVVHDF using the oXiris membrane (40 mL/kg/hour). Mean (SD) treatment duration was 79 (25) hours. Following treatment, a significant increase in mean arterial pressure was observed.5

***p < 0.001. AKI, acute kidney injury; CVVHDF, continuous veno-venous hemodiafiltration; SD, standard deviation.

**Note:** Findings from preclinical, single-arm, and observational studies have not been confirmed in randomized controlled trials. Some data are preliminary and have not been peer reviewed.
Potential for improved organ function and hemodynamic stability

Summary of single-arm, observational studies: Improved organ function and hemodynamic stability following CRRT with the oXiris membrane

<table>
<thead>
<tr>
<th>Study</th>
<th>CRRT modality</th>
<th>Decreased SOFA score</th>
<th>Increased arterial pressure</th>
<th>Reduced norepinephrine dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prospective observational study in adults with AKI due to infection with Gram-negative bacteria (n = 6), compared with historical controls (n = 24)⁸</td>
<td>oXiris membrane-CVVH</td>
<td>✓ After 48 hours*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prospective observational study in postoperative cardiac patients with renal failure and sepsis/septic shock (n = 25)⁷</td>
<td>oXiris membrane-high volume HDF</td>
<td>✓ After 72 hours***</td>
<td>✓ After 72 hours**</td>
<td>✓ After 72 hours**</td>
</tr>
<tr>
<td>Prospective observational pilot study in adults with AKI caused by sepsis or septic shock (n = 34)⁵</td>
<td>oXiris membrane-CVVHDF</td>
<td>✓ After treatment*** (average duration 79 hours)</td>
<td>✓ After treatment*** (average duration 79 hours)</td>
<td>✓ After treatment*** (average duration 79 hours)</td>
</tr>
<tr>
<td>Prospective observational study in patients with renal failure and sepsis/septic shock (n = 40)⁶</td>
<td>oXiris membrane-high volume HDF</td>
<td>✓ After 24 hours*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Summary of observational studies that have reported statistically improvements in organ function (SOFA score) and hemodynamic stability following CRRT with the oXiris membrane.

*p < 0.05; **p < 0.01; ***p < 0.001 versus baseline.

AKI, acute kidney injury; CRRT, continuous renal replacement therapy; CVVHDF, continuous veno-venous hemodiafiltration; CVVH, continuous veno-venous hemofiltration; HDF, hemodiafiltration; SOFA, Sequential Organ Failure Assessment.

Findings from observational studies suggest that, for some patients with AKI, CRRT using the oXiris membrane may have a positive effect on clinical outcomes – organ function and hemodynamic stability.⁵-⁸ The association between these outcomes and inflammatory mediator removal is uncertain.⁵-⁷

Note: Findings from preclinical, single-arm, and observational studies have not been confirmed in randomized controlled trials. Some data are preliminary and have not been peer reviewed.
Clotting and clogging are potential reasons for loss of filter patency, reduced CRRT circuit life, and treatment interruptions

- Filter clogging is thought to occur when proteins and cells are deposited on the membrane, leading to:
  - Blockage of hollow fibers
  - Reduced membrane permeability leading to reduced filter efficacy
  - Increased transmembrane pressure.

- Filter clotting is a common complication encountered during traditional CRRT with heparin anticoagulation. Filter clotting results in:
  - Patient blood loss
  - Reduced dialysis dose delivery
  - Treatment interruptions for filter changes and increased workload for care providers.
Survey: Frequency of clinical and technical complications encountered during renal replacement therapy in patients with AKI\textsuperscript{20}

A survey of practice patterns among clinicians dedicated to critical care nephrology and renal replacement therapy in patients with acute renal failure was conducted at an international nephrology meeting. Results from 560 completed questionnaires suggested that filter clotting was the most common technical complication encountered during CRRT, while bleeding was a common clinical complication.\textsuperscript{20}

CRRT, continuous renal replacement therapy; IHD, intermittent hemodialysis.

The inner surface of the oXiris membrane is grafted with heparin – how may this distinctive feature reduce thrombogenicity?

Designed to inhibit coagulation locally by adsorbing and enhancing the anticoagulatory potency of antithrombin III

- During CRRT, contact between blood and the foreign surface of the extracorporeal circuit initiates a coagulatory response that can lead to filter clotting.\(^{10}\)

- The permanent grafting of heparin onto the inner surface of the oXiris membrane is designed to reduce thrombogenicity by adsorbing antithrombin III (ATIII) from the blood and facilitating formation of a stable complex with thrombin.\(^{2}\)

- With release of the stable ATIII-thrombin complex into the bloodstream, it has been proposed that the heparin graft catalyzes the conversion of ATIII from a weak to a potent anticoagulant.\(^{2}\)

- This proposed mechanism of action has been investigated in vitro.\(^{2}\)
Designed to reduce thrombogenicity

In vitro study: The oXiris membrane has affinity for ATIII\(^2\)

![Graph showing adsorption relative value vs. ATIII concentration, µg/mL](image)

In an adsorption experiment, affinity for biotinylated ATIII was found to be greater with the heparin-grafted oXiris membrane than the non-heparin-grafted AN 69 ST membrane.\(^2\)

ATIII, antithrombin III.

In vitro study: The oXiris membrane promotes formation of ATIII-thrombin complex in vitro\(^2\)

![Graph showing concentration of stable ATIII-thrombin complex formed, ng/mL vs. thrombin concentration, units/mL](image)

The formation of ATIII-thrombin complex after incubation of the oXiris and AN 69 ST membranes with ATIII followed by thrombin has been investigated in vitro. Stable ATIII-thrombin complex formation was found to be greater with the heparin-grafted oXiris membrane than the non-heparin-grafted AN 69 ST membrane.\(^2\)

The heparin graft on the inner surface of the oXiris membrane is intended to reduce thrombogenicity by adsorbing ATIII from the blood and enhancing its anticoagulatory potency at a local level.\(^2\)

Evidence from in-vitro investigations supports this proposed mechanism of action.\(^2\)
The **oXiris** set used with anticoagulation therapy may provide clinically acceptable filter life span for CRRT

In a very small, prospective case series of six patients with sepsis-induced AKI undergoing CVVH using the **oXiris** membrane with regional citrate anticoagulation, the life-span of the hemofilter was 61 hours.\(^4,8\)

\(^4\)No conclusions on the relative anticoagulant effects of the heparin graft on **oXiris** versus the regional citrate anticoagulation regimen can be drawn based on this study.

## Anticoagulation during CRRT

- Administration of systemic or regional anticoagulation is generally required in CRRT to achieve effective treatment by preventing filter clotting and/or reduced membrane permeability.\(^18\)
- However, many critically ill patients with AKI have impaired blood clotting capabilities and are at increased risk for serious bleeding.\(^20-22\)
- The clinical practice guideline from KDIGO (Kidney Disease: Improving Global Outcomes) suggests that:\(^18\)
  - Systemic anticoagulation with heparin is avoided during CRRT in patients with increased bleeding risk
  - Regional citrate anticoagulation is used during CRRT in patients with increased bleeding risk, and for patients without impaired coagulation or increased bleeding risk (where there is no contraindication to citrate).

**Used in combination with regional citrate anticoagulation, the oXiris membrane may support CRRT efficiency by reducing membrane thrombogenicity**\(^2\) and offering clinically acceptable filter life,\(^8\) potentially minimizing treatment interruptions.\(^17,20\)

### Note:
Findings from preclinical, single-arm, and observational studies have not been confirmed in randomized controlled trials. Some data are preliminary and have not been peer reviewed.
What treatments can be delivered via the oXiris set?

- The oXiris set is indicated for use with the Prismaflex system to provide CRRT and fluid management in patients with AKI, fluid overload, or both.
- This single set can be used in a choice of four CRRT modalities, and with either heparin or regional citrate anticoagulation.
- For critically ill patients with AKI, potential advantages of slow, continuous removal of toxins and excess fluid during CRRT compared with more rapid treatment with intermittent renal replacement therapy may include:
  - Greater hemodynamic stability
  - Easy control of fluid balance
  - User-friendly systems.

“We suggest using CRRT, rather than standard intermittent RRT, for hemodynamically unstable patients (2B).”

*KDIGO clinical practice guideline*
A single set offering a choice of CRRT modalities for managing critically ill patients with AKI

The **oXiris** set has diffusive, convective and adsorptive properties, allowing it to clear both small- and medium-to-larger-sized molecular weight solutes from the blood via continuous hemodialysis and continuous hemofiltration modalities.\(^2,^{23}\)

- The oXiris set offers flexibility in the treatment of AKI -- a single set that can be used to support renal function and fluid management via a choice of CRRT modalities, and choice of anticoagulation therapy,\(^2\) to suit patient requirements.
- Since 2009, more than 15,000 patients globally have been treated using the oXiris set.\(^24\)
Combines three functionalities in a single set

Designed to simplify multiple treatment challenges

How might the oXiris set help ease CRRT delivery for your critically ill patients with AKI?

By combining multiple features and functions in a single device, CRRT using the oXiris set may help to improve treatment efficiency and clinical outcomes for critically ill patients with AKI.1,2,4–8

CRRT using the oXiris set may offer potential handling benefits for care providers

- Simple incorporation into the familiar Prismaflex system with same set up as traditional CRRT1
- Should require no change in clinical practice or requirement for staff training
- Can be used in a choice of CRRT modalities1
- Can be used with either heparin or regional citrate anticoagulation
- No additional equipment required for removal of inflammatory mediators1,25,26
- May help to provide clinically acceptable filter life,8 with potential to minimize treatment interruptions17,20 and support adequate dialysis dose delivery18,19
References

oXiris membrane composition and microstructure

Adsorption of inflammatory mediators

Potential for improved organ function and hemodynamic stability

Combines three functionalities in a single set

Designed to simplify multiple treatment challenges

Permanent heparin graft

Local inhibition of coagulation

Designed to reduce membrane thrombogenicity

AN-69-based membrane with diffusive, convective and adsorptive properties

Delivery of hemodialysis and hemofiltration

Supports renal function and fluid management

Baxter, AN 69, AN 69 ST, oXiris, and Prismaflex are trademarks of Baxter International Inc., or its subsidiaries.

EUMP/MG146/15-004 April 2016