CUNO Application Brief

Endotoxin Control For Hemodialysis Water Using Positively Charged Microfiltration

Introduction

Water quality is receiving more and more attention as a key factor in hemodialysis delivery and patient outcome. Dialysis clinics invest heavily in water purification equipment to improve the chemical and microbiological quality of their water. Typical water treatment systems include water softeners, carbon filtration, Reverse Osmosis (RO) and sometimes deionization (DI). The final stage in this purification cascade is an endotoxin filter to control potential bacteria and endotoxin contamination.

Recent developments in dialysis have brought a higher focus to control of bacteria and endotoxin in dialysis feed water:

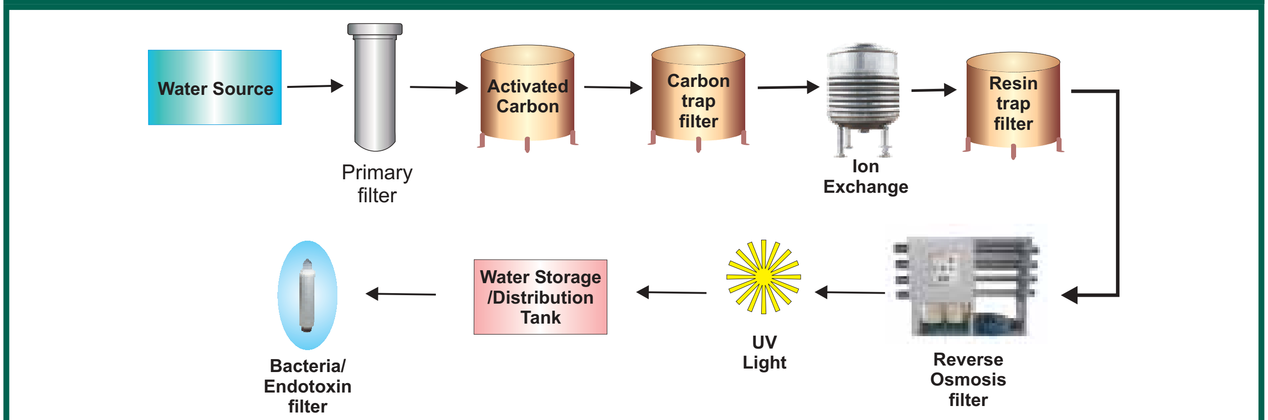
- In 2001, the Association for the Advancement of Medical Instrumentation (AAMI) released a new standard for water treatment equipment for hemodialysis. The new standard (RD-62) added endotoxin limits to the requirements for dialysis feed water quality. The standard set a maximum limit of 2 EU/ml and an action level of 1 EU/ml. This was in addition to the limits for bacteria of 200 CFU/ml and an action level of 50 CFU/ml.
- In March of 2004, AAMI published a draft of their new standard for dialysate for public comment. This new standard (RD-52) set the same bacteria and endotoxin limits for dialysate (200 CFU/ml and 2 EU/ml) as those for water for dialysis.
- Numerous studies and published articles have described the increasing indirect evidence that chronic exposure to low amounts of endotoxin may play a role in some of the long-term complications of hemodialysis therapy (ANSI/AAMI RD62:2001). Patients treated with ultrafiltered dialysate have demonstrated a decrease in serum β2-microglobulin concentrations (Quellhorst E., et al.1998), and a decrease in markers of inflammation (Schindler R, et al. 1994). In longer-term studies, use of microbiologically ultrapure dialysate has been associated with a decreased incidence of β2-microglobulin-associated amyloidosis (Baz M., et al. 1991; Kleophas W, et al.1998: Schwalbe S., et al.1997).

The trend is clear. As the awareness of the effects of endotoxin in dialysis is growing, the standards are tightening.

The Process

The figure below shows a typical hemodialysis water purification system. A bacteria and endotoxin retentive filter is used as a final water purification step.

Figure 1. - Hemodialysis Water Process



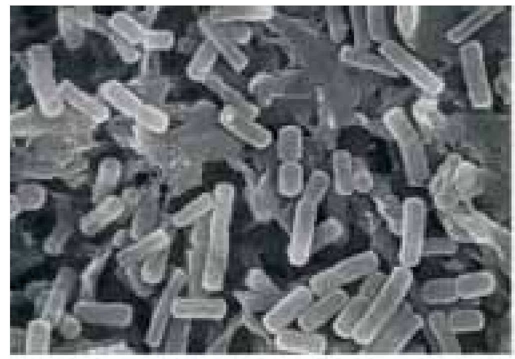
The Challenge

Control of bacteria and endotoxin contamination from hemodialysis water treatment systems requires routine system monitoring, establishment of action limits and procedures for maintenance of each unit operation in water purification. AAMI standards (RD-52) for hemodialysis water quality established action limits for endotoxin levels of 1 EU/ml and 50 CFU/ml for bacteria. In addition to regular maintenance of water system deionization columns and installation of ultraviolet lights, filters are used to remove bacteria and endotoxin contamination. Selection of the most efficient filter requires demonstrated endotoxin removal capability, high water flow rate capability and economical operation.

The Solution

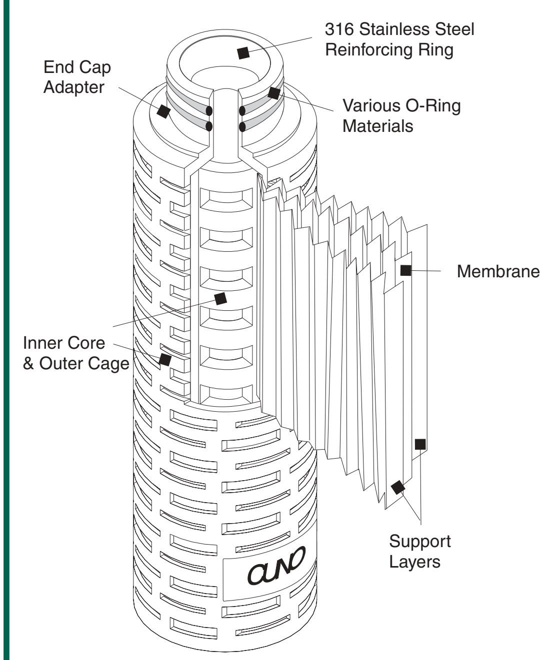
Membrane filters can be used for effective bacteria and endotoxin removal. These filters remove contaminants from liquid streams by size exclusion and adsorption mechanisms. Size exclusion mechanisms involve removal of bacteria and endotoxin contaminants if the membrane filter pore sizes are smaller than the bacterial and endotoxin contaminants. Figures 2 shows Gram negative, rod shaped bacteria.

Figure 2. - Gram Negative, Rod Shaped Bacteria



Compared to endotoxin molecules, bacteria are relatively large in size (1.2 x 0.8 micron) and are removed by absolute rated 0.2 micron sterilizing grade filters. The pharmaceutical industry has used membrane filters for many years to produce bacteria free drugs. These membrane filters are typically constructed with polymeric membranes that are pleated into cylindrical cartridge configurations. Most membrane filter cartridge seal points involve thermoplastic welds directly joining the membrane and cartridge hardware components. The use of adhesives in membrane filter cartridge construction is avoided in order to prevent the potential for breakdown of adhesives that can contaminate the fluid being filtered. An example of a membrane filter cartridge is shown in Figure 3.

Figure 3. - Pleated Membrane Filter



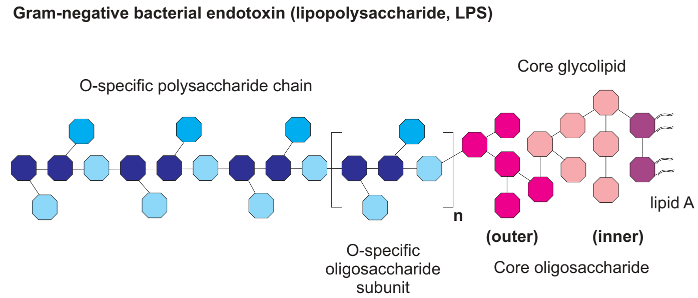
Sterilizing grade membrane filters have carefully controlled pore sizes that reliably retain bacteria predominantly by size exclusion mechanisms. Exclusion by membrane filter pore size has been demonstrated as an effective means of removing bacteria. Endotoxin, however, can be significantly smaller than typical 0.2 or 0.05 micron filter pores, making size exclusion by microfiltration less than ideal for endotoxin removal. Additional filtration capability is needed.

Contaminants smaller than the membrane pore size can be removed by adsorptive retention mechanisms. One way to enhance small contaminant removal is through electrokinetic or charge based adsorption. By treating the surface of polymeric membranes to provide them with a positive charge, the adsorptive forces for negatively charged contaminants is greatly increased. CUNO Incorporated.has developed a positively charged membrane filter called Zetapor®SP. CUNO Zetapor SP filters are qualified for absolute bacteria removal and reduction of endotoxin levels from process fluids such as water.

Other filter types can also be used for hemodialysis water filtration. AAMI standard RD-52 references that hollow fiber ultrafilters can be used for endotoxin removal from water systems. Hollow fiber filters consist of bundles of small fibers through which water flows into the interior or lumen of each fiber and flows out through the fiber walls. Some hollow fiber filters can also be operated in the reverse flow direction. Hollow fiber filters can be operated in cross flow or single pass mode.

A comparison of a pleated membrane filter (CUNO Zetapor SP) and a hollow fiber filter commonly used in dialysis water treatment was performed to evaluate endotoxin removal. Endotoxin molecules are fragments of Gram negative bacterial cell walls and are thus much smaller in size than bacteria. A schematic of an endotxin molecule is shown in Figure 4.

Figure 4. - Endotoxin Molecule



Both filter types are used to filter carbon and DI treated water and to remove low levels of endotoxins that might be present in the water. The filters are used for as much as 20 hours a day to filter room temperature water, and they are sanitized for four hours each night by flowing 90°C water through them.

Laboratory scale tests using representative scale down configurations of both filter types were conducted to compare their efficiency of endotoxin removal. Each filter configuration was challenged with endotoxin spiked Sterile Water for Injection (SWFI) at a test flow rate designed to equal a production flow rate of 8 liters per minute per 10- inch cartridge filter (8 LPM/10- inch). Following the initial challenge, each test filter was flushed with 90°C SWFI for 4 hours and the endotoxin challenge was repeated using the initial challenge conditions. The test challenge conditions are summarized in Table 1.

Table 1. - Test Challenge Conditions

Test Parameter	CUNO Zetapor 020SP	Hollow Fiber Filter
Test filter area	12.6 cm^2	550 cm^2
Challenge Endotoxin Level	5 EU/ml	5 EU/ml
Carrier Solution	Sterile Water for Irrigation	Sterile Water for Irrigation
Total Challenge Volume	100 ml	2200 ml
Scale up volume	60 l	60 l
Test Flow Rate	0.95 l/ft^2/min. (13 ml/min/disc)	0.5 l/ft^2/min. (300 ml/min/unit)
Scale up flow rate/10- inch	8 LPM	8 LPM
Scale up EU challenge	3 $x10^5$ EU	3 $x10^5$ EU

The results of the endotxin challenge tests are shown in Table 2.

Table 2. - Endotoxin challenge: CUNO Zetapor SP Filter vs. Hollow Fiber Filter

CUNO Zetapor 020SP	Inlet Endotoxin (EU/ml)	Outlet Endotoxin (EU/ml)	Percent Removal (%)
Disc #1			
Challenge #1	3.00	< 0.03	> 99.0
Challenge #2	3.00	< 0.03	> 99.0
Disc #2			
Challenge #1	3.00	< 0.03	> 99.0
Challenge #2	3.00	< 0.03	> 99.0
Hollow Fiber Filter	**Inlet Endotoxin (EU/ml)**	**Outlet Endotoxin (EU/ml)**	**Percent Removal (%)**
Filter #1			
Challenge #1	3.00	0.30	90.0
Challenge #2	3.00	0.30	90.0
Filter #2			
Challenge #1	3.00	0.30	90.0
Challenge #2	3.00	0.60	80.0

In all tests, the endotoxin concentration in CUNO Zetapor 020SP filtrate was below detectable limits. Results with the hollow fiber filter indicated the presence of detectable endotoxin in all filtrate samples.

Summary and Conclusion

There is an increasing need for improvement of water quality in treatment of dialysis patients. More rigorous standards are being established for acceptable limits and action limits for bacteria and endotoxin levels in dialysate water. This paper summarizes data comparing endotoxin removal efficiency for two types of filters used as final filters in water systems: a pleated membrane filter having a positive surface charge (CUNO Zetapor SP) and a hollow fiber membrane filter.

The results of the study showed that the CUNO Zetapor 020SP filter achieved >99% removal of all upstream endotoxin, to below detection limits, (<0.03 EU/ml) both before and after exposure to a 90°C hot water cycle. The hollow fiber filters demonstrated a 90% removal of upstream endotoxin prior to the 90°C hot water cycle. Following the 90°C hot water exposure, the endotoxin removal performance of the hollow fiber filters ranged from 80 to 90% removal.

The results demonstrate greater efficiency of endotoxin removal was obtained with the CUNO Zetapor SP filter as compared to the hollow fiber filter. It is also noteworthy that the CUNO Zetapor SP filter is constructed without the use of adhesive materials to seal the filter cartridge. Upon continued exposure to hot water used to sanitize hemodialysis water systems, adhesive components can weaken and result in loss of filter integrity. Adhesive components can also be extracted by continued exposure to water and can leach into water used for dialysis patients.

The advantages of using a state-of-the-art CUNO pleated membrane filter cartridge having a positive surface charge has been demonstrated in terms of increased efficiency for endotoxin removal. The CUNO filter is also constructed without adhesive components providing durability and low extractables in water systems.

References:

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