CHAPTER 140

Membranes and Filters for Use in Acute Renal Failure

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OBJECTIVES

This chapter will:

1. Describe the main components of filter and membranes for continuous renal replacement therapy (CRRT).
2. Characterize the performance parameters of filters and membranes.
3. Describe the fundamentals of solute and fluid transport in CRRT.

Renal support for acute kidney injury (AKI) relies on various dialysis methods whose origin may be traced to methods used primarily in the treatment of end-stage renal disease (ESRD) or to Kramer's seminal work in the development of continuous renal replacement therapy (CRRT).[1] Methods of treatment may be intermittent or continuous and include the use of a filter to allow solute and fluid removal from the patient by various combinations of diffusion, convection, adsorption, and ultrafiltration. In this chapter, the physical properties and functional performance of devices and membranes are discussed.

HISTORY AND EVOLUTION OF FILTERS AND MEMBRANES

Filters for renal replacement therapy have been designed over the years to have properties allowing for adequate solute and fluid exchange.[2] Since the beginning of dialysis, filter design has featured a two-compartment structure consisting of a blood compartment and an effluent compartment, separated by a semipermeable membrane. (The effluent compartment collects fluid comprising various combinations of dialysate, replacement fluid, and net ultrafiltrate, depending on the prescribed modality.) Initially, devices in which the membrane in the form of a tube was made

from unmodified cellulose wound around a rotating drum were used (Fig. 140.1).

Today, treatment is undertaken with specially designed equipment used almost exclusively in conjunction with a hollow-fiber device (Fig. 140.2) or, very uncommonly, a parallel-plate device.

Plate and hollow-fiber devices have been developed in an attempt to obtain the best configuration for ideal countercurrent solute exchange (Fig. 140.3).

Blood ports with conic or spiral distributors have been designed to obtain an even distribution of the flow in all available spaces of the blood compartment. When filters are used as dialyzers in the hemodialysis mode, they have to be supplied with inlet and outlet dialysate ports. The dialysate compartment generally is designed to provide uniform flow with minimal trapping of bubbles and reduced stagnation or channeling of dialysis fluid. The introduction of fiber spacer yarns and specific fiber undulation (periodicity) have been technical developments designed to achieve such flow and to optimize the countercurrent configuration.[3]

In parallel-plate dialyzers, several layers of flat sheet membranes are stacked, supported by thin plates. The major (theoretical) advantage of plate over hollow-fiber dialyzers is lower resistance to blood flow. On the other hand, the volume of the blood compartment in plate devices varies according to the pressures applied and may be unacceptably high in some patients.

Hollow-fiber dialyzers overcome many of the limitations imposed by plate devices and offer the best compromise between blood volume and surface area exposed for exchange. However, the major limitation of the hollow-fiber design is the higher blood compartment resistance, leading to more complex fluid mechanics in the filter.

Overview on Devices and Membranes

The contemporary design of hollow-fiber dialyzers consists of a single fiber bundle contained in a housing made of biocompatible materials (e.g., polycarbonate, polyethylene). The bundle is encapsulated ("potted") at both ends with a silicone material before being sterilized and put in the

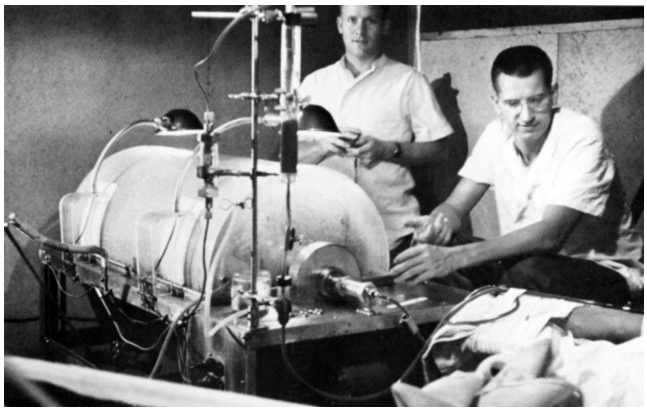

FIGURE 140.1 Early (c. 1950) treatment of acute renal failure using the Kolff-Brigham dialysis system.

FIGURE 140.2 A series of modern hollow-fiber hemodialyzers of differing surface area suitable for use in the treatment of chronic and acute renal failure. The devices shown use fibers with a three-dimensional microwave structure incorporated into a specifically designed housing to provide optimized flow distributions in the blood pathway and the dialysate pathway. (Photograph courtesy Fresenius Medical Care, Bad Homburg, Germany.)

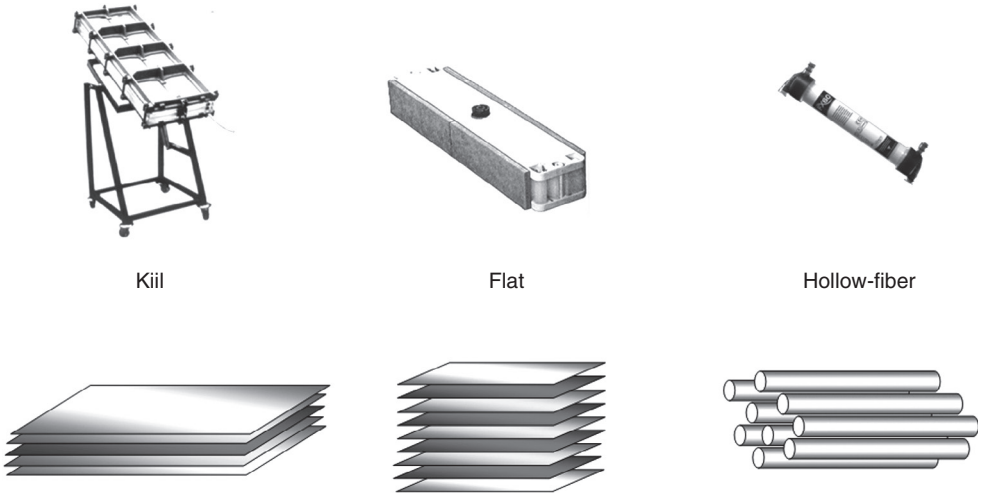

FIGURE 140.3 The evolution of hemodialyzers. Hemodialyzers can have a plate configuration or hollow-fiber configuration. In either case, the unit consists of three main components: the blood compartment, the membrane, and the dialysate compartment.

Synthetic	DIAPES™ AN69™ AN69ST Polyamix™ Toraysulfone™ αPolysulfone	Rexeed™ PEPA™ Fresenius Polysulfone™ PAN Arylane™ PMMA
Modified cellulose	Cellulose-diacetate Cellulose-triacetate HEMOPHAN™	SMC™ EXCEBRANE™ PEG-RG
Unmodified cellulose	CUPROPHAN™ SCE	Cuprammonium rayon

FIGURE 140.4 The clinically used range of membranes.

housing. Two caps cover the end surfaces of the bundle at both sides. The housing contains inlet and outlet ports for blood (directly on the housing or on the end caps) and one or more additional ports for the effluent compartment, depending on the mode for which the filter is conceived. Based on a specific manufacturer's approach, blood flow enters the filter in parallel with respect to the fiber bundle. The design, size, and geometric characteristics of the fiber bundle are the primary determinants of the performance characteristics for the entire filter.

Because of the size of the global market, most filter development activities have occurred for chronic hemodialysis therapy. Different bundle configurations have been developed in the past to maximize treatment efficiency, including rectangular block arrangements, cross-flow configurations, multiple bundles, spiral fibers surrounding a central core, and warp-knitted hollow-fiber mats.[4] Today, the most common configuration is the Moiré structure, in which an undulation of the fiber bundle with a specific periodicity is applied.[5]

The major geometric characteristics of hollow fibers are length, mean inner radius, and wall thickness. The porosity of the whole bundle, an important determinant of diffusive solute removal in conventional hemodialysis, is determined by the pore density (number of pores/unit surface area) in each fiber multiplied by the total number of fibers in the bundle.

This and other membrane properties influence several filter characteristics, which are important considerations when prescribing a certain therapy, including surface area, filter priming volume (volume of blood compartment), and total priming volume (sum of volumes of blood and effluent compartments).

Membrane Materials

The most important parameter determining the chemical and physical behavior of a membrane is the material of which it is composed. A wide spectrum of filters together with a multitude of different membrane materials are currently available on the market.[6]

In Fig. 140.4 the main materials that make up membranes used for dialysis are summarized. Dialysis membranes can

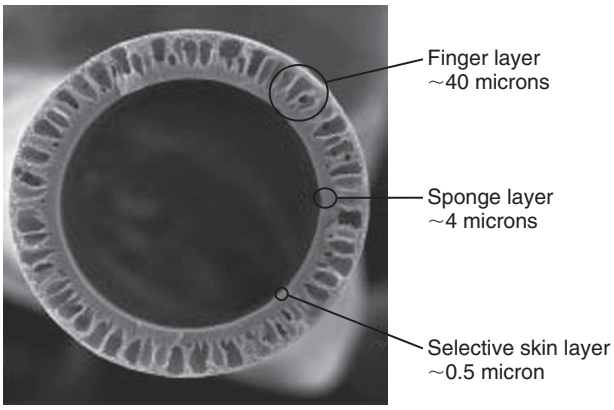

FIGURE 140.5 Synthetic membrane structure.

be classified according to their chemical structure. Natural and synthetic polymers are used currently worldwide for this application because of their characteristics of chemical resistance, sterilizability, industrial processing, and biocompatibility.

Natural polymeric membranes can be further subclassified as unmodified cellulose based and modified cellulose based. In the latter category, hydroxyl groups (–OH) have been reduced by substitution (e.g., cellulose acetate) or by bonding of synthetic materials to the cellulose. In chronic hemodialysis, the use of unmodified cellulosic membranes now is exceedingly rare and the use of synthetic membranes continues to increase.

Membranes applied for CRRT are almost exclusively synthetic. Synthetic polymers for membranes are classified as thermoplastics. This class of materials results in less complement activation with respect to natural polymers such as cellulose because of their hydrophobic nature. Almost all synthetic polymers currently used for CRRT are hydrophobic: the exception is AN69. Hydrophobic membranes in general are relatively biocompatible but typically require a hydrophilic pore-enlarging agent (e.g., polyvinylpyrrolidone, PVP) to achieve the desired permeability.

In general, synthetic polymeric membranes have an asymmetric structure (Fig. 140.5); again the exception

here is AN69. A typical asymmetric membrane wall is at least 20 μm in thickness and consists of a thin (~1 μm) inner "skin" layer in contact with the blood compartment. This layer is the primary determinant of the solute removal properties for the membrane. The remainder of the membrane wall is characterized by a much thicker spongy region, with interstices that cover a wide size range, as determined by the manufacturing process and the polymer composition.

Contemporary synthetic membranes can be manufactured with a relatively sharp curve of pore size distribution, allowing closer simulation of the filtration provided by the native kidney and greater removal of middle-high molecular weight molecules. Modern high-flux membranes, in the "virgin" state, allow filtration of molecules reaching almost 50 to 60 kDa while restricting the passage of albumin to a great extent.

Device Performance

Solute transport across membranes occurs by two different mechanisms: diffusion and convection. In addition, there also can be an interaction between the solutes and the membrane surface, leading to their binding (adsorption).

The relative contributions to total solute transport from diffusion and convection are determined by the treatment modality. For example, in hemodialysis the dominant mode of solute transport is diffusion, whereas convection is the prevailing mechanism in hemofiltration. Adsorption occurs with all treatment modalities and can be considered either as a negative attribute (membrane fouling leading to a reduction in transmembrane transport) or a positive attribute (removal of low-molecular proteins or peptides).[7]

Mathematically, diffusive solute transport across the membrane is governed by Fick's law, depending largely on the concentration gradient of the solute between the blood compartment and the dialysate side.[8] On the other hand, convective transport is transmembrane solute movement resulting from the bulk movement of solvent in the presence of a pressure gradient ("solvent drag").[9] Adsorption reflects the interaction at a molecular level between the material surface and the molecule; it is determined by the hydrostatic forces and the nature of the compound.[10] It can be quantified by either the Freundlich equation or the more commonly used Langmuir equation for monolayer adsorption on a surface. These equations are based on a number of assumptions, including (1) adsorption can only occur at a fixed number of definite localized sites; (2) each site can hold only one molecule; (3) all sites are equivalent with no interaction between adsorbed molecules.

PERFORMANCE PARAMETERS

Membrane Ultrafiltration Coefficient

The membrane ultrafiltration coefficient K_{UF} represents the water permeability of a filter per unit of pressure and surface area; it is defined as

$$K_{UF} = \frac{Q_{UF}}{TMP} \cdot \frac{1}{A}$$

and measured in mL/hr/mm Hg/m^2. Q_{UF} is the ultrafiltration flow rate (mL/hr), *TMP* is the transmembrane pressure (mm Hg), and *A* is the membrane surface area (m^2).

Filter Ultrafiltration Coefficient

The product of membrane ultrafiltration coefficient and membrane surface area is defined as the filter ultrafiltration coefficient DK_{UF}[11]:

$$DK_{UF} = K_{UF} \cdot A$$

and its unit of measure is [mL/hr/mm Hg]. Its value, with the operating parameters of the treatment (summarized by transmembrane pressure), helps define the ultrafiltration and convective solute removal properties of the filter.

Sieving Coefficient

Solute sieving coefficient (SC) is defined as the ratio of the solute concentration in the ultrafiltrate (C_{UF}) to the solute concentration of bulk plasma water (C_W)[12]:

$$SC = \frac{C_{UF}}{C_W}$$

In practice, the sieving coefficient may be calculated as follows:

$$SC = \frac{2C_{UF}}{C_{Wi} + C_{Wo}}$$

where the subscripts *Wi* and *Wo* represent the concentration of bulk plasma water at the inlet and the outlet of the filter, respectively.

In the absence of protein binding, the solute concentration in plasma water is related to the plasma concentration as follows[13]:

$$\frac{C_p}{C_w} = 1 - \varphi$$

where ϕ is the volume fraction of hydrated proteins and is 0.07 of the concentration in plasma (C_P).
The concentration in the blood is related to that in plasma by the following formula:

$$\frac{C_p}{C_w} = 1 - HCT + \lambda \cdot HCT$$

where λ is the distribution coefficient between red cells and plasma and HCT is the hematocrit.

Cutoff and Retention Onset

The cutoff of a specific membrane represents the molecular weight of the smallest solutes retained by the membrane; it depends on average membrane pore size and pore size distribution. The statistical cutoff value is defined as the molecular weight of the solute having an SC of 0.1.

On the other side, the retention onset represents the molecular weight of a molecule with an SC of 0.9. Essentially, this value corresponds to the size of a solute whose passage through the membrane begins to have some restriction by the pore structure (i.e., 10% constraint). For a complete understanding of the performance characteristics of a membrane, the cutoff value and the retention onset must be taken into account, allowing evaluation of the profile of the SC curve for each membrane.[14]

Clinically, the expression "high cutoff" describes membranes with a cutoff value that approximates the molecular weight of albumin.

Clearance

Dialytic solute transport in the clinical setting frequently is characterized quantitatively by clearance (K), a term analogous to the clearance concept of the human kidney.[15] It focuses on solute removal by the device and can be defined as "the amount of solute removed from the blood per unit of time (N), divided by incoming blood concentration (C_B)" (i.e., the volumetric rate of mass removal by the device):

$$K = N/C_B$$

When solute clearance is estimated with this equation, a steady-state assumption typically is made, implying that net solute generation is balanced by net removal. For continuous depuration processes (e.g., endogenous kidney function), the indexing of mass removal rate to blood concentration allows for patients with widely varying kidney function to be compared with the same standard.

Clearance determinations can be derived from estimations of either blood-side or dialysate/effluent-side mass removal rates, and the approach is modality-specific. For example, urea removal in conventional hemodialysis typically occurs at a high rate, leading to a substantial difference between the incoming (inlet) and outgoing (outlet) urea blood concentrations for the filter. As such, the classic methodology for estimating instantaneous filter clearance for conventional HD is expressed mathematically:

$$K_B = \frac{(Q_{Bi} \times C_{Bi}) - (Q_{Bo} \times C_{Bo})}{C_{Bi}} + Q_{UF} \times \frac{C_{Bo}}{C_{Bi}}$$

because

$$Q_{Bi} - Q_{Bo} = Q_{UF}$$

where K_B is whole blood clearance, Q_B is blood flow rate, C_B is whole blood solute concentration, and Q_{UF} is net ultrafiltration rate. (The subscripts *i* and *o* refer to the inlet and outlet blood lines.)

Clearance Determinations for Continuous Renal Replacement Therapy

The operating conditions during CRRT lead to a different set of considerations. A defining characteristic of CRRT is the reduced rate at which solute and net fluid removal occur in comparison to conventional HD. The relatively low efficiency of CRRT renders unhelpful blood-side instantaneous clearance determinations because blood passage through the filter does not produce substantial differences between the incoming and outgoing blood concentrations. Thus, when an instantaneous clearance is determined for a CRRT filter, effluent measurements (product of the flow rate and solute concentration) are used to estimate the numerator of the standard clearance equation (i.e., mass removal rate).

Mass Transfer Area Coefficient K_0A

The mass transfer area coefficient, K_0A, represents the overall capacity of the membrane to diffusively remove solute over the entire filter surface.[16] It is the product of the membrane surface area (A) and the overall mass transfer coefficient (K_0). In general, K_0A is used to characterize filters used for efficient therapies (e.g., conventional HD) but not for CRRT filters.

The K_0A, in countercurrent configuration, can be calculated experimentally as

$$K_0A = \frac{Q_B \cdot Q_D}{Q_B - Q_D} \ln\left[\frac{Q_D(Q_B - K)}{Q_B(Q_D - K)}\right]$$

CLASSIFICATION OF MEMBRANES AND FILTERS

The traditional classification of membranes has been on the basis of K_{UF} value. It generally is assumed that "low-flux" membranes have K_{UF} < 10 mL/hr/mm Hg/m^2, "high-flux" membranes are characterized by K_{UF} > 25 mL/hr/mm Hg/m^2, and middle-flux membranes have an ultrafiltration coefficient between 10 and 25 mL/hr/mm Hg/m^2.

However, a more rigorous classification incorporating solute and water permeability properties has been proposed recently. The scheme includes traditional low-flux and high-flux categories along with a more recently developed class of high cutoff ("super-high-flux") membranes. This latter class has "virgin" water permeability values that are approximately two- to fivefold and an order of magnitude greater than those of traditional high-flux and low-flux membranes, respectively. In comparison to traditional high-flux membranes, high cutoff membranes demonstrate substantially higher SCs for molecules as large as albumin. On one hand, this characteristic allows for much higher clearances of solutes in the low-molecular-weight protein class (e.g., many inflammatory mediators). However, albumin loss is a relevant consideration, largely confining the use of these membranes to diffusive modalities. This classification scheme, displayed in the context of MWRO and MWCO values, is shown in Table 140.1.[14]

FACTORS INFLUENCING TREATMENT PERFORMANCE

Solute transport during extracorporeal treatments is function of blood, dialysate, and ultrafiltration flow rates (Fig. 140.6). In general, CRRT employs lower blood flow rates than conventional hemodialysis; in parallel, dialysate and ultrafiltration flows are reduced substantially. Diffusive clearance in CRRT is not influenced substantially by blood flow rate but instead is determined primarily by filter surface area and dialysate flow rate. On the other hand, solute removal efficiency in predilution and postdilution continuous veno-venous hemofiltration (CVVH) is influenced substantially by the attainable blood flow rate. However, blood flow frequently is limited in the acute setting because of vascular access dysfunction.

In particular, ultrafiltration across the membrane during treatment is governed by the presence of a pressure gradient

TABLE 140.1

Classification of Membranes and Filters Based on Structural Characteristics

	STRUCTURAL CHARACTERISTICS		
DIALYZER TYPE	MWRO (kDa)	MWCO (kDa)	PORE RADIUS (nm)
Low-flux	2–4	10–20	2–3
High-flux	5–10	25–65	3.5–5.5
Protein leaking	2–4	60–70	5–6
High cutoff	15–20	170–320	8–12

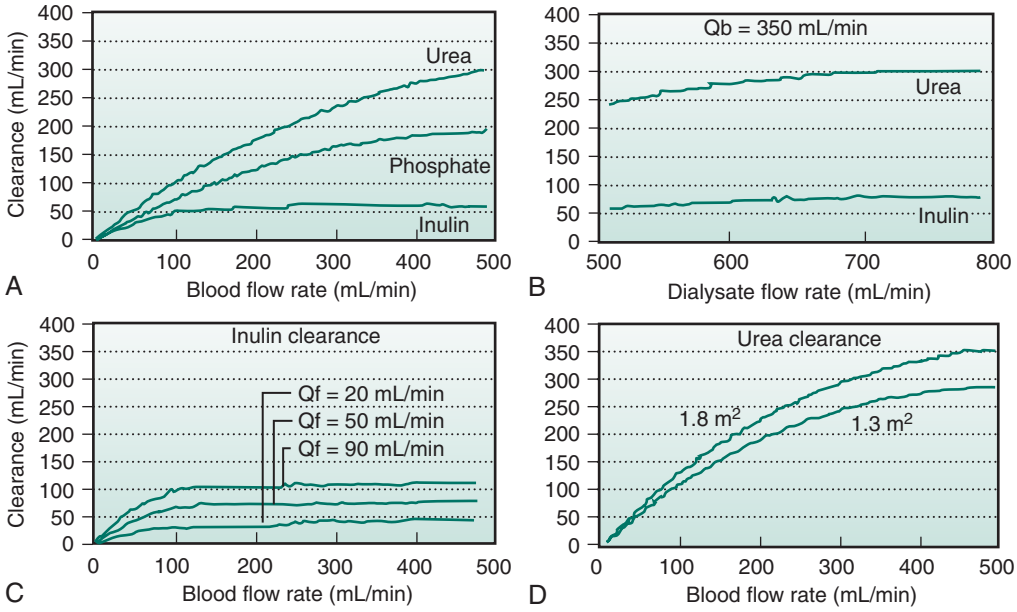

FIGURE 140.6 The influence of operating parameters on clearance characteristics. A, Influence of blood flow rate (Q_B) at a constant dialysate flow rate on the clearance of small and large molecules. B, Influence of varying the dialysis fluid flow rate on the clearance of small and large molecules. C, Influence of flux on the clearance of large molecules. D, Influence of surface area on the clearance of small molecules. *Qf,* Ultrafiltration flow rate.

and the plasma oncotic pressure. The dependence of ultrafiltration on the fluid dynamic conditions within devices is complex and has not been studied extensively. In filters applied for convective therapies, the ultrafiltration flow rate is dependent on the shear rate or the velocity gradient at the blood-membrane interface, which in turn is influenced by the local hematocrit along the length of the filter. Shear rate is directly proportional to blood flow rate for blood flow rates used in dialysis therapies. As such, shear effects (and the associated attenuation of concentration polarization and secondary membranes effects) tend to be less in CRRT in relation to conventional HD.

The relationship between flow and pressure in a tube is governed by the Hagen-Poiseuille law, which, in the context of a hollow-fiber blood pathway, can be expressed as follows:

$$\Delta P = \frac{128\mu L}{\pi N d_i^4} Q_B$$

where μ is the blood viscosity, L is the length, N is the number of fibers, d_i is the internal diameter of the fibers, and Q_B is the blood flow rate.

This relationship is critically dependent on the blood pathway dimensions. In particular, the pressure is dependent on the fourth power of the fiber diameter. In practical terms, this means that a 10% variation in fiber diameter will result in a 46% variation in flow through the fibers.

Membrane fouling, concentration polarization, and thrombus generation are three phenomena that can influence the solute transport substantially. As suggested above, these phenomena are particularly pronounced in CRRT because of the relatively low blood flow rates used.

SELECTION OF FILTERS AND MEMBRANES

The selection of filters and membranes is linked not only to the delivery of treatment dose and the role that the membrane may play in outcomes but also to the treatment regimen used. Although the maintenance of fluid balance and improved vascular stability favor the use of continuous treatment modalities, circuit patency and fluid removal rates tend to decrease with elapsed treatment time and may necessitate the application of strategies to prolong performance and patency.[17]

As is the case in chronic dialysis, small solute removal is used as an adequacy parameter in the management of AKI patients.[18,19] Over the past decade, blood flow rates and filter membrane surface areas have increased to allow for delivery of the higher CRRT doses recommended by consensus standards. However, CVVH continues to be the most challenging modality to achieve adequate small solute clearance. Indeed, for predilution and postdilution CVVH, azotemia control may not be adequate in some hypercatabolic patients if a blood flow rate of at least 200 mL/min cannot be achieved. In such patients, continuous venovenous hemodialysis (CVVHD) or continuous venovenous hemodiafiltration (CVVHDF) may be a better option.

In addition to adequate removal of small molecular compounds, clearance of larger molecular weight compounds (e.g., inflammatory mediators) may be desirable. The removal of inflammatory mediators is favored by the use of high-permeability membranes, convective mass transport, and membranes in which there is significant removal by adsorption.[20]

Experimental and clinical studies have suggested that dialysis membrane biocompatibility may influence the morbidity and mortality of patients with AKI, and complement activation by dialysis membranes also may prolong the recovery from AKI. As discussed elsewhere, however, meta-analyses relating biocompatibility to treatment outcomes have not found an unequivocal benefit for synthetic membranes over unsubstituted cellulose membranes.[21]

FUTURE DEVELOPMENTS

Recent innovations in the field of biomaterials and membranes for CRRT have led to interest in the use of new

devices. In comparison with conventional filters, the desired attributes of these new devices are increased biocompatibility and reduced thrombogenicity and biologic reactivity with the blood, enhanced selectivity with approximation of glomerular filtration. Vitamin E–coated membranes may be used to reduce the oxidative stress,[22] surface-treated membranes can reduce anticoagulation needs and increase the filter life span,[23] and high cutoff membranes are able to provide higher clearance for high-molecular-weight solutes and inflammatory mediators.[24]

CONCLUSION

This chapter provides a general overview of membranes and filters applied in the management of AKI patients. The structural features determining the properties of hollow-fiber filters used for AKI dialysis therapies have been discussed. In addition, the performance parameters used to characterize filter performance have been presented. Finally, the basic mechanisms by which solute and water removal occur have been described. All of these issues are important for the prescribing clinician to understand so that AKI therapies can be prescribed rationally.

Key Points

1. A big variety of membranes are currently available for renal replacement therapy applications. The main determinants are materials, structural and geometric characteristics, and modalities for which they are intended to be applied.
2. Diffusive transport is affected mainly by blood and dialysate flow rates, whereas convective transport and ultrafiltration are influenced primarily by the pressure gradient across the membrane and by its hydraulic permeability.
3. Performance parameters of membranes and filters, such as the membrane ultrafiltration coefficient, filter ultrafiltration coefficient, sieving coefficient, cutoff, and retention onset, are determinants for the choice of a correct personalized therapy.
4. Membranes reducing thrombogenicity and oxidative stress, enhancing the selectivity with approximation of glomerular filtration and specific high cutoff membranes, are the main current developments for improving clinical outcomes in AKI patients undergoing extracorporeal therapies.

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