SEMINARS IN
NEPHROLOGY

Dialyzer Membranes as Determinants of the Adequacy of Dialysis

Madhukar Chelamcharla, John K. Leypoldt, and Alfred K. Cheung

Hemodialysis membranes have undergone a gradual but substantial evolution over the past few decades. Classification of modern dialyzer membranes by chemical composition bears little relationship to their functional characteristics. The fundamental properties that determine the capacity of the membrane to remove solutes and fluids are its surface area, thickness, pore size, pore density, and potential to adsorb proteins. Dialyzer membrane performance is characterized clinically by its efficiency, defined as the potential to remove urea and presented as the mass-transfer area coefficient (KoA) and ultrafiltration coefficient (K_{uf}),defined as the potential to remove water adjusted for the transmembrane pressure. The parameter K_{uf} usually, but not invariably, correlates with the membrane permeability, defined as the potential to remove middle molecules, with β_2-microglobulin being the currently popular marker. The sieving coefficient reflects the membrane potential to transport solutes by convection and is particularly useful for hemofiltration. Enhancing solute clearance is accomplished clinically by increasing blood and dialysate flow rates, strategies that also are applicable to middle molecules for highly permeable membranes. Novel designs of dialyzers include the optimization of fluid flow path geometry and increasing the membrane pore selectivity for solutes by using nanotechnology.
Semin Nephrol 25:81-89

Hemodialysis is the major form of renal replacement therapy in the United States and many parts of the world. As of December 2002, the number of patients on chronic maintenance hemodialysis in the United States alone was approximately 300,000,[1] and these numbers are expected to grow significantly in the next decade. Since their introduction half a century ago, dialyzer membranes and dialyzers have undergone many significant advances. Dialyzer membranes have evolved from those based on natural materials such as cellulose to various synthetic membranes with improved biocompatibility characteristics. The efficiency of dialyzers also has improved significantly, allowing greater removal of solutes in a shorter amount of time. Although adequate dialysis is undoubtedly an important factor that determines the outcomes of chronic hemodialysis patients, the optimal level of solute removal that leads to the best clinical outcome has not been defined clearly. This article discusses various types of dialyzer membranes and their characteristics that affect the dose and adequacy of dialysis.

Department of Medicine, University of Utah School of Medicine, Salt Lake City, UT; and Research Service and Medical Service, Veterans Affairs Salt Lake City Healthcare System, Salt Lake City, UT.

Address reprint requests to Alfred K. Cheung, MD, Dialysis Program, 85 North Medical Dr East, University of Utah, Salt Lake City, UT 84112. E-mail: alfred.cheung@hsc.utah.edu

Historical Perspective

The first hemodialysis on a human was performed in 1923 by Haas[2] by using collodion tubes. Kolff and Higgins[3] improved the procedure by using cellophane tubing that originally was used in sausage casings as the dialyzer membrane. In this technique, a cellophane membrane made from cellulose was wrapped around a drum that rotated in a tank of dialysate. This rotating drum dialyzer was the first widely used hemodialysis apparatus. Hemodialyzers have advanced in subsequent years by the development of several alternative designs that include twin-coil dialyzers, parallel-flow dialyzers, and, finally, hollow fiber dialyzers, which is the dialyzer type most commonly used today.

Types of Membranes

Current dialyzer membranes can be broadly classified into 3 types based on their chemical composition: unsubstituted cellulosic membranes, substituted cellulosic membranes, and synthetic membranes (Table 1).

Unsubstituted Cellulosic Membranes

Unsubstituted cellulosic membranes were the only dialyzer membranes used from the 1940s through the 1960s. The

0270-9295/05/$-see front matter
doi:10.1016/j.semnephrol.2004.09.014

Table 1 Classification of Dialyzer Membranes Based on Chemical Composition

Membrane Category	Chemical Composition
Unsubstituted cellulosic	Regenerated cellulose
	Cuprammonium cellulose
	Cuprammonium rayon
	Cuprammonium rayon coated with polyethylene glycol
Substituted cellulosic	Cellulose acetate
	Cellulose diacetate
	Cellulose triacetate
	Hemophan
	Synthetically modified cellulose or (polysynthane)
Synthetic	Polyacrylonitrile
	Polyacrylonitrile copolymerized with methalyl sulfonate (AN69)
	Polyamide
	Polycarbonate
	Polyethylene polyvinyl alcohol
	Polymethylmethacrylate
	Polysulfone
	Polyethersulfone

original cellophane membranes were made of cellulose, which is a polysaccharide derived from pressed cotton. Cuprammonium membranes regenerated from cellulose were used extensively in the 1960s and still are used in some parts of the world, primarily because of their lower cost. Cuprammonium membranes were practical because they could be made thin, mechanically strong, and provided reasonable diffusive transport of small uremic toxins, such as urea and creatinine.[4] Their low mean pore size, however, renders them less effective in removing larger molecules.

Substituted Cellulosic Membranes

Unsubstituted cellulosic membranes have hydroxyl groups on their glucosan rings, which appears to be responsible for their propensity to activate the complement system via the alternative pathway when these proteins come into contact with blood. This activation of complement is partially responsible for the subsequent activation of neutrophils and other leukocytes, making these membranes bioincompatible.[5]

The replacement of these surface hydroxyl groups with acetate groups in cellulose acetate membranes decreases complement activation, thereby increasing biocompatibility, at least by the criteria of complement and neutrophil activation. The first of this type of membrane was cellulose monoacetate, in which many of the free hydroxyl groups were replaced by acetate residues. These were followed by the development of cellulose diacetate and triacetate membranes with more than three-fourths substitution of the hydroxyl groups, leading to further decreases in complement activation.[6]

Hemophan (Gambro Renal Products, Lakewood, IL) is another cellulose-based membrane in which free hydroxyl groups are replaced by diethylaminoethyl moieties. Although this substitution is less than 5%, the diethylaminoethyl groups are capable of masking the hydroxyl groups, thereby decreasing complement activation by virtue of their size and spatial arrangement.[7] These substituted membranes also have the advantage of being hydrophobic compared with the hydrophilic unsubstituted cellulosic membranes. More recently, cellulosic membranes with other substitutions, such as the benzyl groups, have become available (synthetically modified cellulose).[8]

Synthetic Membranes

Several synthetic membranes with high water permeability were developed in the 1960s, primarily for the purpose of hemofiltration (Table 1).[9] Compared with the thin and symmetric cellulosic membranes, these membranes are thick ($\geq$20 μm) and may be either symmetric (eg, AN69; Hospa) or asymmetric (eg, polysulfone). The asymmetric composition of the latter membranes refers to the 2-layered structure of the hollow-fiber wall when viewed in cross-section, with an inner thin layer that comes into contact with the blood and plays a major role in regulating solute removal and a thick supporting stroma. The chemical and structural composition of the stroma varies and dictates thermal and mechanical properties of the membrane.[10] Early synthetic membranes were very hydrophobic, resulting in excessive adsorption of plasma proteins onto their surfaces. To circumvent this problem, polyvinylpyrrolidone has been added to the manufacturing process to decrease their hydrophobicity.[11] The addition of polyvinylpyrrolidone may also affect the pore size distribution of synthetic membranes and increase the susceptibility of the membranes to modifications during reprocessing of dialyzers for reuse.

Physical Characteristics that Determine Membrane Performance

The membrane characteristics are the most important determinants of the dialyzer performance. Other factors, such as the geometry of the membrane fibers that influence the blood and dialysate flow patterns and shear rates at the fluid-membrane interface, also influence dialyzer performance. The performance of the membrane per se, and the transport parameters associated with the membrane, are, in turn, dependent on the following properties: pore size, surface area, membrane thickness, pore density, and protein adsorption.

Pore Size

An ideal dialyzer membrane should closely resemble the glomerulus in its filtration properties and allow the transport of uremic solutes with a broad range of molecular weights, without allowing the loss of serum albumin and other physiologically beneficial proteins. The pore size is the most important determinant of the membrane to achieve this tight control of solute transfer. The early unsubstituted cellulosic membranes had very small pores and allowed for the transport of only water and small-molecular-weight solutes, such

as urea and creatinine, with little or no removal of uremic toxins of molecular weights greater than 1,000 d. The development of substituted cellulosic and synthetic membranes with larger pore sizes allowed the removal of larger solutes. The current membrane manufacturing techniques integrate various scientific disciplines, including polymer chemistry and nanotechnology, to design synthetic membranes that allow more selective removal of uremic toxins.

Pore size is also the most important determinant of ultrafiltration of water. The relationship between these 2 can be explained with the Hagen-Poisseuille equation, assuming that all the pores have a cylindric shape:[10]

$$R = 8\ \mu L/\pi r^4, \quad (1)$$

in which R is the resistance to ultrafiltrate flow through a single pore, μ is the viscosity of ultrafiltrate, L is the thickness of the membrane, and r is the radius of the pore. From this equation, one can see that a small increase in the pore radius will decrease the flow resistance to a great extent. Current commercial dialyzer membranes cannot be manufactured with pores of a single uniform size; thus, all membranes contain pores of various sizes. The most selective dialyzer membranes have pore size distributions that are narrow, with the majority of pores of approximately the same size.

Surface Area

The surface area of a dialyzer is a function of length and inner diameter of the individual hollow fibers and the total number of hollow fibers in the dialyzer. One advantage of small fiber diameter is the decrease in the thickness of the unstirred layer of blood at the membrane-blood interface, thus minimizing the boundary layer effect, which in turn leads to increased transmembranous diffusion of solutes. Unfortunately, very narrow hollow fibers are disadvantageous at that same time, which also can be explained by the Hagen-Poisseuile equation.[10] According to this formula, the flow of liquid through a cylinder or hollow fiber can be calculated as:

$$Q_B = \Delta P/(8\ \mu L/\pi r^4), \quad (2)$$

in which Q_B is the blood flow rate, ΔP is the axial pressure decrease, μ is the blood viscosity, L is the fiber length, and r is the hollow fiber radius. Another way of expressing this equation is as follows:

$$Q_B = \Delta P/R, \quad (3)$$

in which R is the resistance to the blood flow through the hollow fiber. From these equations, it can be deduced that

$$R = 8\ \mu L/\pi r^4 \quad (4)$$

Equation 4 shows that a small decrease in the hollow fiber radius will increase the resistance to blood flow to a great extent, thus requiring higher hydrostatic pressure to perfuse the fibers. Another disadvantage of very narrow hollow fibers is the increased potential for thrombosis. The usual dimensions of hollow fibers in current dialyzers are 20 to 24 cm in length and 180 to 220 μm in inner diameter. From these values, the internal surface area of an individual fiber can be calculated by using the formula:

$$A = 2\pi rL, \quad (5)$$

in which A is the surface area, r is the radius, and L is the length of the fiber. Currently, large-surface-area dialyzers have approximately 12,000 fibers in each dialyzer. The internal surface area of the dialyzer can be obtained by multiplying the total number of fibers in a dialyzer with the internal surface area of each fiber. The surface area of currently used large dialyzers exceeds 2 m^2.

Membrane Thickness

The initial cellophane membrane was 20 to 40 μm in thickness. The substituted cellulosic membranes used nowadays are much thinner, with thicknesses of approximately 8 μm, thus allowing improved mass transport. Contrary to the symmetric and thin cellulosic membranes, asymmetric synthetic membranes contain a thin skin layer that comes in contact with the blood and a thick support layer that provides structural support to the skin layer. The pore size of the support layer is 2 to 3 times that of the skin layer. Therefore, the support layer is not a major selective barrier to solute transfer, although it may provide a diffusion barrier to certain solutes because of its thickness.

Pore Density

The pore density of a dialyzer membrane is an important determinant of water flux and solute clearance. Uremic toxins often are classified based on their molecular weights. Middle molecules traditionally have been defined as uremic toxins with molecular weights in the range of 500 to 5,000 d. This range later was extended to include solutes with higher molecular weights, in part because of the recognition that many proteins with molecular weights less than that of albumin (60,000 d) are retained in kidney failure and possess potential toxicity. β_2-microglobulin (β_2M; 11,800 d) is a protein in this category and is a commonly used marker at present for the assessment of middle-molecule clearance of dialyzers.

In general, the water flux and permeability for middle molecules of a membrane are directly related to each other, so that a membrane with high water flux also has high permeability to middle molecules. On a theoretic basis, however, this relationship does not always hold true. A membrane that has a very large number of small pores, either as a result of high pore density or large surface area, will have high water flux (high flux), but may have low permeability to middle molecules.

Protein Adsorption

Although many uremic solutes and water are removed from the blood by means of diffusion and convection, peptides and small proteins are removed by adsorption to the surface of the membrane during hemodialysis. Adsorption occurs primarily within the pore structures rather than on the nominal membrane surface that comes into contact with the blood.[12]

Table 2 Effect of Changing Dialyzer Blood Flow Rate on Urea Clearance

	KoA (mL/min)	K at Q_b 250 (mL/min)	K at Q_b 450 (mL/min)	% Change in K From Q_b 250 to Q_b 450
Conventional	400	150	177	+18%
High efficiency	1,000	200	263	+32%

NOTE. Dialysate flow rate was assumed to be 500 mL/min.

Therefore, a membrane with high pore density and large pores but a small surface area could adsorb more proteins than a membrane with a high surface area but low pore density and small pores. Another characteristic that affects adsorption is the hydrophobicity of the membrane; the more hydrophobic the membrane is, the higher the adsorptive capacity. In dialyzers containing membranes that avidly adsorb proteins, quantification of the dialysate proteins alone would substantially underestimate the removal of the protein by the dialyzer. Adsorption is also at least partially responsible for the prevention of back-transfer of endotoxins and other cytokine-inducing substances from the dialysate to the blood compartment.

Clinical Terms Used to Characterize Membrane Performance

The following terms are used clinically to characterize dialyzer performance.

Efficiency

By convention, the term *efficiency* refers to the capacity of the dialyzer to remove low-molecular-weight uremic solutes. Urea is by far the most extensively studied marker of these solutes. The mass transfer area coefficient (KoA), expressed in mL/min, for a given solute is the clearance of the dialyzer at infinitely high blood and dialysate flow rates on a theoretical basis. Therefore, KoA is a measure of the maximum solute removal capacity of the dialyzer and conceptually has been considered as an intrinsic property of the dialyzer membrane.

KoA values for urea usually are provided in the manufacturers' brochures for dialyzers. Current dialyzers are classified into high-efficiency and low-efficiency types based on their urea KoA. A high-efficiency dialyzer has a KoA value of greater than 600 mL/min, whereas a low-efficiency dialyzer has a KoA value of less than 450 mL/min. These definitions are arbitrary and have not been sanctioned by regulatory agencies. KoA per se has little value for individual patients because it is not possible to attain these infinitely high flow rates in clinical practice. KoA values should be used primarily only for the purpose of comparing different dialyzer models, but not as absolute measures of their clinical performance.

Mathematic formulae and nomograms are available to estimate the urea clearance (K) of a particular dialyzer at a given blood flow rate and dialysate flow rate, based on the dialyzer's KoA value.[13] The dialyzer K value for urea increases with the blood flow rate, although the relationship is not linear and depends on the type of membrane and the design of the dialyzer. With an increase in blood flow rate, the K value of a low-efficiency dialyzer increases only modestly because the low efficiency of the dialyzer, and not the blood delivery to the dialyzer, is the limiting factor under these conditions. This concept can be shown by comparing the change in the urea clearances of 2 hypothetical dialyzers with different KoA values at 2 different blood flow rates using the urea clearance formula proposed by Daugirdas et al[14] (Table 2).

At a blood flow rate of 250 mL/min (Q_b 250), the clearance K is 150 mL/min for the hypothetical low-efficiency dialyzer, with a KoA of 400 mL/min and a dialysate flow rate of 500 mL/min. When the dialyzer blood flow rate is increased from 250 mL/min to 450 mL/min (Q_b 450), the K achieved by the same dialyzer and the identical dialysate flow rate increases from 150 to 177 mL/min, representing an increase of 18%. In contrast, the K of the arbitrary high-efficiency dialyzer with a KoA value of 1,000 mL/min is 200 mL/min at a Q_b of 250 mL/min and the identical dialysate flow rate. This Q_b is low for the high-efficiency dialyzer. In other words, the capacity of the dialyzer to remove urea has not been exploited fully because of the low delivery rate of blood and its urea content to the dialyzer. When the Q_b is increased from 250 to 450 mL/min, there is a substantial increase (32%) in K, to 263 mL/min. Therefore, a high-efficiency dialyzer should be used to derive the maximum benefit from increasing Q_b.

When a dialyzer of very high efficiency is used, the limiting factor may no longer be the dialyzer itself; instead, the blood flow rate through the vascular access and the ability of the heart to tolerate the extracorporeal blood flow become the critical determinants. Similar to the clearance of free solutes such as urea and creatinine, the clearance of protein-bound solutes recently has been shown to increase by using high KoA dialyzers and by increasing the dialysate flow rate.[15]

Permeability

By convention, the permeability of a dialyzer membrane usually denotes the capacity of the membrane to clear middle molecules. It should be noted that, besides molecular weight, the charge and other physicochemical properties of the molecule also determine the clearance by a certain dialyzer membrane. High-permeability membranes have clearance values of greater than 20 mL/min for β_2M. In contrast, the β_2M clearances of low-permeability membranes are less than 10 mL/min, and often are approximately zero (Table 3). Note that the definition of membrane permeability for β_2M defined here does not take into consideration the dialyzer blood flow rate and dialysate flow rate. These clearance values apply to usual operating conditions in US dialysis centers that in-

Table 3 Comparison of Functional Parameters of Conventional, High-Efficiency and High-Flux Dialyzers

Functional Parameters	High Efficiency	High Flux	Conventional (Low Efficiency, Low Flux)
KoA urea	>600 mL/min	Variable	<450 mL/min
K_{urea}*	>200 mL/min	Variable	<200 mL/min
K_{uf}	Variable	>12 mL/h/mm Hg	<12 mL/h/mmHg
$K_{\beta 2M}$*	Variable	>20 mL/min	<10 mL/min

NOTE. Except for the definitions of high flux and low flux, which are provided by the Food and Drug Administration, the other definitions are arbitrary and provided by the HEMO study or the current authors.

Abbreviations: K_{urea}, urea clearance; $K_{\beta 2M}$, β_2M clearance.

*Under usual operating conditions (see text for explanation).

clude a blood flow rate of 300 to 450 mL/min and a dialysate flow rate of 500 to 800 mL/min. Although these flow rates have little impact on β_2M clearances by low-permeability membranes, they significantly could affect the clearance by high-permeability membranes in a manner similar to, albeit to a lesser extent than, their effect on urea clearance. Therefore, it might be necessary to characterize membrane permeability more precisely in the future, even for clinical comparisons. For example, β_2M clearances could be evaluated at specific blood and dialysate flow rates. Alternatively, KoA values for β_2M could be determined.

Sieving Coefficient

The sieving coefficient (S) is another measure of the membrane's capacity to clear solutes. Unlike permeability, which is more reflective of the diffusive transport properties, S is reflective of the convective transport properties. It is calculated as follows:

$$S = C_f / C_p, \quad (6)$$

in which C_f and C_p are the solute concentrations in the ultrafiltrate and the plasma water, respectively, determined in a purely convective mode.[16] An S value of 1.0 indicates that the solute is not hindered in its movement across the membrane, and solute concentrations in both compartments therefore are identical. The S value is dependent on the mean pore size of the membrane, the molecular weight, and the configuration of the solute. The S value of low-molecular-weight solutes, such as urea and potassium, almost always is close to unity, but the S value decreases as the molecular weight of the solute increases. Knowledge of the S value for various solutes is particularly useful in the setting of hemofiltration in the intensive care unit, where the removal of drugs in the extracorporeal circuit occurs primarily by convection.

Ultrafiltration

Ultrafiltration refers to the transfer of water across the dialyzer membrane. The ultrafiltration coefficient (K_{uf}) is calculated in milliliters of ultrafiltrate per hour per mm Hg of transmembrane pressure (TMP). A membrane with a very high K_{uf} will need a very low TMP to filter a large amount of water. It should be noted that the term K_{uf} is not normalized to membrane surface area; therefore, dialysis membranes that have small pores potentially could have a high K_{uf} if the surface area is very large. The official classification of dialyzer membranes by the Food and Drug Administration is based on the K_{uf}.[17] According to this classification, dialyzer membranes are divided into high-flux and low-flux categories (Table 3).High-flux membranes have K_{uf} values of greater than 12 mL/h/mm Hg, and as high as 80 mL/h/mm Hg. Low-flux membranes have K_{uf} values less than 12 mL/h/mm Hg. The hemodialysis (HEMO) study further defines high-flux membranes as those with β_2M clearances of greater than 20 mL/min and low-flux membranes as those with β_2M clearance of less than 10 mL/min.[18] This definition was chosen arbitrarily to achieve clear separation between the 2 treatment groups with regard to β_2M clearances.

The terms *flux* and *permeability* often are used interchangeably, even though they are not always directly related to each other, as explained earlier when describing the concept of pore density. In vitro K_{uf} values reported by manufacturers often are overestimates of the in vivo values by 3% to 5%. This overestimation is partly owing to the differences in the nature of the solution used in the testing. For example, values obtained using whole bovine blood are expected to be lower than those obtained using crystalloid solutions. This dependence of dialyzer performance on the nature of the testing solution also applies to other membrane transport parameters, such as KoA and the S value.

Although the early cellulosic membranes were low flux, membrane flux is independent of its chemical composition in most modern dialyzers. Cellulosic membranes can be made into either low flux or high flux, and synthetic membranes also can be either low flux or high flux. Table 3 provides a general comparison of the transport characteristics of conventional, high-efficiency, and high-flux dialyzers.

High-flux dialysis has 3 clinically important consequences that should be considered.

Volume Control

By definition, high-flux membranes remove large quantities of fluid with only relatively low TMP, which could lead to excessive fluid removal and intravascular volume depletion if the TMP is not controlled tightly. Modern dialysis machines have automated systems that accurately control the ultrafiltration rate and volume. The K_{uf} of the dialyzer membrane is almost never a determinant of the ability to remove fluid from the patient. For example, even with a K_{uf} of 10 mL/h/mm Hg, a TMP of 200 mm Hg (which is attained readily) would be sufficient to remove 2 L of fluid in an hour or 8 L of fluid in

4 hours. The major hindrance is the plasma fluid refilling capacity of the patient.

Back-Transfer

Another consequence of high-flux dialysis is back filtration,[19] which can be explained as follows. As the blood enters the arterial or afferent end of the dialyzer, there is a higher intraluminal pressure inside the hollow fiber compared with the dialysate side. This leads to ultrafiltration of fluids so that the pressure within the lumen of the hollow fiber decreases toward the venous or efferent end and actually will become less than the pressure in the dialysate compartment at that point. This axial pressure decrease will allow ultrafiltration of water from the high-pressure dialysate compartment to the low-pressure blood compartment. This phenomenon of back-transfer is partly responsible for the transport of endotoxins and other contaminants from the dialysate side to the blood compartment. Hydrophobic synthetic membranes have been shown to adsorb some of the dialysate contaminants and minimize the contamination of the blood that occurs during the back-transfer process.

Albumin Loss

A third concern regarding the use of high-flux membranes relates to the nonselectivity of the membranes. Although a larger pore size is helpful in removing middle molecules, the possibility of losing albumin from the plasma also increases with high-flux dialysis.[20] With the availability of super high flux membranes with very high permeability, this potential complication is even more likely. Some researchers have advocated the removal of some albumin to remove toxins that are bound to this plasma protein. Although there is limited information about the clinical significance of serum albumin loss associated with the dialysis membranes, the loss of a large amount of albumin, to remove the proportional amount of albumin-bound toxins, is likely to be deleterious. The use of predilutional hemofiltration to dissociate the toxins from albumin is probably a more reasonable approach. Further studies are needed to address this important issue.

Effect of Re-Use on Membrane Performance

Dialyzer re-use is a common practice in the United States, with 80% of dialysis centers using reprocessed dialyzers,[21] although it is practiced in less than 10% of the centers in Europe[22] and prohibited in Japan.[23] The characteristics of various membranes may change on re-use of the dialyzers, depending on the chemical structure of the membrane and the type of reprocessing method used.

Re-use leads to the decrease of effective surface area of the dialyzers as a result of blood clotting in some of the hollow fibers, sometimes causing an incomplete delivery of the prescribed dialysis dose. This led to the concept of total cell volume (TCV), also known as fiber bundle volume. Gotch[24] showed that dialyzers lose less than 10% of small-solute clearance if the TCV of the reprocessed dialyzer is maintained at more than 80% of its initial value. Current guidelines from the Centers for Disease Control and Prevention and the Association for the Advancement of Medical Instrumentation mandate that the re-used dialyzers should have a urea clearance that is at least 90% of its initial value or at least 80% TCV. The 80% TCV requirement, however, was based historically on data generated from low-flux membrane dialyzers that were disinfected using formaldehyde only. As new synthetic membranes and newer germicides, such as glutaraldehyde, peracetic acid, heat, and citric acid, came into use, the relationship between TCV and membrane performance became less clear. Several later studies showed that this criterion of 80% TCV also applied to high-flux synthetic membranes,[25,26] however, these studies involved only a very small number of patients. Data from the HEMO study showed that when high-flux membranes were reprocessed, the loss of urea clearance was almost double that of low-flux membranes (-1.9% versus -1.0% after 10 re-uses).[18] The relationship between the loss of urea clearance and the number of re-uses appeared to be linear, at least up to 20 re-uses. The use of Renalin (Minntech Corporation, Minneapolis, MN) as a germicide decreased the urea clearance the most, especially in high-flux cellulose triacetate dialyzers (-2.9% per 10 re-uses).

There is a poor relationship between the degree of loss in small-solute clearance and the change in middle-molecule clearance on dialyzer reuse. The effect of re-use on middle-molecule clearance varies greatly, depending on the type of membrane and the type of reprocessing method used.[26,27] In the HEMO study, when Renalin alone was used as the germicide, β_2M clearances by the high-flux cellulose triacetate membranes (CT190, Baxter Healthcare Corporation; Deerfield, IL) decreased more than 50% after 10 re-uses. In contrast, there was a substantial increase in β_2M clearance by polysulfone membranes (F80B, Fresenius Medical Care; Lexington, MA) when bleach was used in conjunction with a germicide. Reprocessing of dialyzers using bleach also has been shown to increase albumin leakage by high-flux polysulfone membranes, although the magnitude of this leakage appears to be small for the newer polysulfone membranes.[28]

These differences in dialyzer performance associated with re-use likely reflect the various effects of the reprocessing reagents on membrane pore structures and fiber paths of the dialyzers. These observations indicate the need for collecting more information regarding the effect of re-use on solute clearances, especially for middle molecules with different molecular weights and potential toxicities. As the understanding of uremic toxins increases and the clearances of middle molecules are targeted more precisely, the TCV criterion developed for urea clearance probably will be insufficient in the monitoring of performance during dialyzer reuse.

Adequacy of Dialysis

This article focuses on dialyzer membranes as determinants of dialysis adequacy, rather than attempting to define dialysis adequacy precisely.

Small-Solute Clearance

The National Cooperative Dialysis Study was the first randomized controlled study that examined the effect of urea clearance on clinical outcomes in chronic hemodialysis patients.[29] Based on the results of the National Cooperative Dialysis Study, the concept of urea Kt/V for quantification of dialysis was developed and became the standard for prescribing and monitoring the chronic hemodialysis dose.[30] For the past 2 decades, dialysis adequacy in the United States largely has emphasized urea clearance. Initially, a urea Kt/V value of 0.85 was thought to be sufficient. As data from observational studies accumulated in subsequent years, a higher Kt/V appeared to be associated with a decrease in mortality, at least up to a Kt/V of 1.2 to 1.3.

Whether a further increase in urea Kt/V confers survival advantage remains a matter of controversy. Observational studies have suggested that increasing dialysis dose greater than the current Kidney Disease Outcome Quality Initiatives guidelines improves patient survival.[31-33] In the primary analysis of the HEMO study, however, there was no statistically significant difference in all-cause mortality between patients who were randomized to the standard dose (with achieved single-pool urea Kt/V of 1.32) and those who were randomized to the high dose (with achieved single-pool urea Kt/V of 1.71) during 3-times-per-week hemodialysis. Subgroup analysis of the HEMO study and observational analysis of the US Renal Data System data suggest that higher doses improve patient survival in women, but not in men.[34] This differential effect of high dose does not appear to be owing to differences in body size. Until further information becomes available, it appears reasonable to achieve a single-pool urea Kt/V of 1.25 for men, as suggested by the most recent Kidney Disease Outcome Quality Initiatives guidelines, and consider a higher Kt/V (1.70) for women.

Strategies to increase urea Kt/V to these targets include increasing the dialyzer clearance K and/or the treatment time. The latter can be prolonged to 6 to 8 hours per session, although definitive proof of the benefits of these long dialysis treatments still is pending. Dialyzer urea K can be increased by increasing dialyzer blood flow, dialysate flow, or the KoA of urea. As discussed earlier, an increase in blood or dialysate flow rate does not lead to substantial increases in K unless the KoA of the dialyzer is substantially higher than the blood and dialysate flow rates. The value of increasing blood flow rate is discussed in another article "Vascular Access as a Determinant of Adequacy of Dialysis," in this issue.

The KoA of the dialyzer can be increased by the simultaneous use of 2 dialyzers connected either in parallel or in series. This seldom is necessary nowadays with the availability of very large single dialyzers with KoA values exceeding 1,200 mL/min. Recent innovations in dialyzer design also have enhanced dialyzer efficiency by the placement of multifilament spacer yarns within the fiber bundle and the use of wavy or moiré structuring of the fibers.[35] Such modifications have been shown to increase the urea clearance by up to 20% at similar blood and dialysate flow rates.

Because of its association with vascular calcification and hyperparathyroidism, hyperphosphatemia has received a great deal of attention in recent years. Although dietary restrictions and oral phosphate binders are critical measures of correcting hyperphosphatemia, removal by dialysis also can play an important role, as evidenced by either normalization of serum phosphorus levels or induction of hypophosphatemia by frequent nocturnal hemodialysis.[36,37] Although phosphate is a relatively small molecule, it appears to be better removed by high-flux than low-flux membranes. Nonetheless, the acute changes in serum phosphorus concentration may not be significantly different between high flux and low flux because of the rapid physiologic responses to extracorporeal phosphate removal.

Middle-Molecule Clearance

Despite the widespread popularity of urea Kt/V in the quantification of dialysis dose, it only represents one aspect of dialysis adequacy, that is, clearance of small uremic toxins. The middle-molecule hypothesis, initially proposed in the 1960s, suggested the importance of other uremic toxins with higher molecular weights that are not cleared readily by conventional low-flux cellulosic membranes and do not follow the dialyzer kinetics of urea.[38] In the past few decades, a number of middle molecules with various sizes, physicochemical properties, and in vitro toxicities have been identified.

Observational studies have suggested the benefits of using high-flux membranes, such as the improvement of neutrophil functions and plasma lipolytic activities and lower incidence of amyloidosis and mortality.[39-42] The HEMO study randomized 1,846 patients to either the high-flux or low-flux arm and followed-up these patients for an average period of 4.48 years. The term *flux* used in the HEMO study is essentially the same as the term *permeability* used in this article. There was a clear separation in β_2M clearance between the 2 groups, with mean values of 33.8 mL/min and 3.4 mL/min, respectively. Although the 8% decrease in all-cause mortality in the high-flux arm compared with the low-flux arm was statistically insignificant, the high-flux arm was associated with a statistically significant 20% decrease in cardiac deaths in secondary analysis. The beneficial effects appeared to be more prominent in patients who had been dialyzed for a longer period of time before the study.

Inasmuch as these HEMO data suggest that high-flux dialysis improves long-term clinical outcome, removal of middle molecules is preferable. It should be noted that, despite the clear separation between the 2 arms, the mean β_2M clearance in the high-flux arm (33.8 mL/min) was substantially less than the values that can be achieved and maintained by using certain types of dialyzers and reprocessing methods (60–70 mL/min). Nocturnal dialysis, hemodiafiltration, and sorbent technology are other techniques that can increase middle-molecule clearance further.

As the costs of synthetic high-flux membranes decrease further, the use of these membranes is becoming more common in the United States and many parts of the world. As discussed earlier, increasing dialyzer blood flows may en-

hance middle-molecule clearance when high-flux membranes with very large pore sizes are used. A significant limitation of porous membranes is the loss of plasma albumin and larger proteins. Applications of the advances in polymer science and nanotechnology show promise in the development of selective membranes that provide high middle-molecule clearances while minimizing the loss of larger proteins.

Fluid Removal

The maintenance of the euvolemic state is an important aspect of adequate dialysis. Unfortunately, this is an area that has not been emphasized sufficiently by the practitioners and regulatory agencies, partly because of the lack of a clear definition and tools to assess the optimal volume status and the symptoms that often are encountered in patients undergoing dialytic fluid removal. It is important to reiterate that the dialysis membrane and its K_{uf} are almost never the limiting factors for fluid removal. The limiting factors are usually the plasma refilling rate and tolerance of the patient.

Other Functions of Dialysis Membranes

In addition to the primary function of providing a semipermeable surface for water and solute removal, dialysis membranes have been designed for other purposes. An example of this is membranes that possess antioxidant properties. Oxidative stress is well described in chronic dialysis patients and has been attributed to the uremic milieu, chronic inflammation, and other factors. Hemodialysis may exacerbate the oxidant stress by blood-membrane interactions that lead to complement and leukocyte activation. For example, the activation of neutrophils by unsubstituted cellulosic membranes results in the release of reactive oxygen species.[43] An advancement in decreasing oxidant stress is the development of dialyzer membranes that are coated with α-tocopherol. Several studies have shown that these membranes decrease oxidant stress by various mechanisms.[44,45] Novel concepts and developments similar to this likely will transform the dialysis membrane from a passive to a dynamic structure that is capable of further improving the uremic milieu.

References

1. Annual Report, ESRD Clinical Performance Measures Project. Baltimore, Centers for Medicare and Medicaid Services, 2003
2. Haas G: Dialysis of flowing blood in the patient. Klin Wochenschr 70:1888, 1923
3. Kolff WJ, Higgins CC: Dialysis in the treatment of uremia: Artificial kidney. J Urol 72:1082-1094, 1954
4. Lysaght MJ: Hemodialysis membranes in transition. Contrib Nephrol 61:1-17, 1988
5. Chenoweth DE: Complement activation during hemodialysis: Clinical observations, proposed mechanisms, and theoretical implications. Artif Organs 8:281-290, 1984
6. Grooteman MP, Nube MJ, van Limbeek J, et al: Biocompatibility and performance of a modified cellulosic and a synthetic high flux dialyzer. A randomized crossover comparison between cellulose triacetate and polysulphon. ASAIO J 41:215-220, 1995
7. Schaefer RM, Horl WH, Kokot K, et al: Enhanced biocompatibility with a new cellulosic membrane: Cuprophan versus Hemophan. Blood Purif 5:262-267, 1987
8. Clark WR, Shinaberger JH: Clinical evaluation of a new high efficiency hemodialyzer: Polysynthane. ASAIO J 46:288-292, 2000
9. Streicher E, Schneider H: The development of a polysulfone membrane. A new perspective in dialysis? Contrib Nephrol 46:1-13, 1985
10. Clark WR, Gao D: Properties of membranes used for hemodialysis therapy. Semin Dial 15:191-195, 2002
11. Gohl H, Buck R, Strathmann H: Basic features of the polyamide membranes. Contrib Nephrol 96:1-25, 1992
12. Clark WR, Macias WL, Molitoris BA, et al: Membrane adsorption of beta 2-microglobulin: Equilibrium and kinetic characterization. Kidney Int 46:1140-1146, 1994
13. Daugirdas JT, Van Stone JC: Physiologic principles and urea kinetic modeling, in Daugirdas JT, Blake PG, Ing TS (eds): Handbook of Dialysis (ed 3). Philadelphia, Lippincott Williams & Wilkins, 2001, p 22
14. Urea kinetic modeling: Tables and figures, in Daugirdas JT, Blake PG, Ing TS (eds): Handbook of Dialysis (ed 3). Philadelphia, Lippincott Williams & Wilkins, 2001, p 674
15. Meyer TW, Leeper EC, Bartlett DW, et al: Increasing dialysate flow and dialyzer mass transfer area coefficient to increase the clearance of protein-bound solutes. J Am Soc Nephrol 15:1927-1935, 2004
16. Henderson LW: Biophysics of ultrafiltration and hemofiltration, in Jacobs C, Kjellstrand C, Koch K, et al (eds): Replacement of Renal Function by Dialysis (ed 4). Dordrecht, Kluwer Academic, 1995, pp 114-117
17. Center for Devices and Radiological Health: Guidance for the Content of Premarket Notifications for Conventional and High Permeability Hemodialyzer. Food and Drug Administration, Rockville Maryland, 1998
18. Cheung AK, Agodoa LY, Daugirdas JT, et al: Effects of hemodialyzer reuse on clearances of urea and beta2-microglobulin. The Hemodialysis (HEMO) Study Group. J Am Soc Nephrol 10:117-127, 1999
19. Clark WR: Quantitative characterization of hemodialyzer solute and water transport. Semin Dial 14:32-36, 2001
20. Ikizler TA, Flakoll PJ, Parker RA, et al: Amino acid and albumin losses during hemodialysis. Kidney Int 46:830-837, 1994
21. Tokars JI, Frank M, Alter MJ, et al: National surveillance of dialysis-associated diseases in the United States, 2000. Semin Dial 15:162-171, 2002
22. Fassbinder W, Brunner FP, Brynger H, et al: Combined report on regular dialysis and transplantation in Europe, XX, 1989. Nephrol Dial Transplant 6:5-35, 1991 (suppl 1)
23. Held PJ, Wolfe RA, Gaylin DS, et al: Analysis of the association of dialyzer reuse practices and patient outcomes. Am J Kidney Dis 23:692-708, 1994
24. Gotch F: Solute and water transport and sterilant removal in reused dialyzers, in Deane N (ed): Guide to Reprocessing of Hemodialyzers, Dordrecht, Martinus Nijhoff, 1986, pp 39-63
25. Canaud B, Nguyen QV, Garred LJ, et al: Reuse of "highly permeable" dialyzers with peroxyacetic acid as sole cleansing and disinfecting agent. ASAIO Trans 37:653-657, 1991
26. Ouseph R, Smith BP, Ward RA: Maintaining blood compartment volume in dialyzers reprocessed with peracetic acid maintains Kt/V but not beta2-microglobulin removal. Am J Kidney Dis 30:501-506, 1997
27. Westhuyzen J, Foreman K, Battistutta D, et al: Effect of dialyzer reprocessing with Renalin on serum beta-2-microglobulin and complement activation in hemodialysis patients. Am J Nephrol 12:29-36, 1992
28. Kaysen GA, Dubin JA, Muller HG, et al: Relationships among inflammation nutrition and physiologic mechanisms establishing albumin levels in hemodialysis patients. Kidney Int 61:2240-2249, 2002
29. The National Cooperative Dialysis Study. Kidney Int Suppl S1-122, 1983
30. Gotch FA, Sargent JA: A mechanistic analysis of the National Cooperative Dialysis Study (NCDS). Kidney Int 28:526-534, 1985
31. Parker TF 3rd, Husni L, Huang W, et al: Survival of hemodialysis patients in the United States is improved with a greater quantity of dialysis. Am J Kidney Dis 23:670-680, 1994
32. Bloembergen WE, Stannard DC, Port FK, et al: Relationship of dose of hemodialysis and cause-specific mortality. Kidney Int 50:557-565, 1996

33. Port FK, Ashby VB, Dhingra RK, et al: Dialysis dose and body mass index are strongly associated with survival in hemodialysis patients. J Am Soc Nephrol 13:1061-1066, 2002
34. Port FK, Wolfe RA, Hulbert-Shearon TE, et al: High dialysis dose is associated with lower mortality among women but not among men. Am J Kidney Dis 43:1014-1023, 2004
35. Ronco C, Brendolan A, Crepaldi C, et al: Blood and dialysate flow distributions in hollow-fiber hemodialyzers analyzed by computerized helical scanning technique. J Am Soc Nephrol 13:S53-S61, 2002 (suppl 1)
36. Mucsi I, Hercz G, Uldall R, et al: Control of serum phosphate without any phosphate binders in patients treated with nocturnal hemodialysis. Kidney Int 53:1399-1404, 1998
37. Pierratos A, Ouwendyk M, Francoeur R, et al: Nocturnal hemodialysis: Three-year experience. J Am Soc Nephrol 9:859-868, 1998
38. Scribner B: Evolution of middle molecule hypothesis, in Hea V (ed): Proceedings of Fifth International Congress of Nephrology. Basel, Karger, 1974, pp 190-199
39. Vanholder R, Ringoir S, Dhondt A, et al: Phagocytosis in uremic and hemodialysis patients: A prospective and cross sectional study. Kidney Int 39:320-327, 1991
40. Seres DS, Strain GW, Hashim SA, et al: Improvement of plasma lipoprotein profiles during high-flux dialysis. J Am Soc Nephrol 3:1409-1415, 1993
41. van Ypersele de Strihou C, Jadoul M, Malghem J, et al: Effect of dialysis membrane and patient's age on signs of dialysis-related amyloidosis. The Working Party on Dialysis Amyloidosis. Kidney Int 39:1012-1019, 1991
42. Woods HF, Nandakumar M: Improved outcome for haemodialysis patients treated with high-flux membranes. Nephrol Dial Transplant 15:36-42, 2000 (suppl 1)
43. Himmelfarb J, Lazarus JM, Hakim R: Reactive oxygen species production by monocytes and polymorphonuclear leukocytes during dialysis. Am J Kidney Dis 17:271-276, 1991
44. Satoh M, Yamasaki Y, Nagake Y, et al: Oxidative stress is reduced by the long-term use of vitamin E-coated dialysis filters. Kidney Int 59:1943-1950, 2001
45. Clermont G, Lecour S, Cabanne JF, et al: Vitamin E-coated dialyzer reduces oxidative stress in hemodialysis patients. Free Radic Biol Med 31:233-241, 2001