Hemodialysis Technology

Nuhad Ismail, John R. Brouillette and Salim K. Mujais

Introduction

Hemodialysis (HD), the most prevalent treatment modality for end-stage renal disease (ESRD), has undergone tremendous evolution during the past decade, including mass production of highly efficient dialyzers, availability of sophisticated equipment to control fluid balance and deliver bicarbonate-containing dialysate, and an increase in the percentage of centers that re-use dialyzers. The use of high-flux dialysis has also increased since 1988, as represented by its use in at least 40% of the dialysis centers. The following describes these technologic advances, as well as recent developments in blood-membrane interactions and their clinical sequelae. Since familiarity with the physical characteristics of hollow fiber dialyzers represent an important issue in dialyzer choice, this chapter also provides a brief overview of the most important operating characteristics of hollow fiber dialyzers as well as the most important problems and appropriate solutions associated with their use.

Hollow Fiber Dialyzers

Physical Characteristics

Dialyzers provide a semipermeable surface across which a diffusion gradient is created between a patient's blood volume and a constantly repleted volume of dialysate. Hollow fiber dialyzers are chemically complex, having several compounds incorporated in their structural components: housing material, end cap compartments, potting material and transport surface. When clinical reactions occur, they may be due to material in the dialyzer assembly and not the components of the membrane [1, 2]. Reviewing the physical and chemical components of these units provide the clinician with a better understanding of dialyzer function and interpretation of clinical reaction to dialyzer use.

Geometry

The geometric characteristics of a hollow fiber determine the membrane surface area, which can be varied by changing the number of fibers, their length, and their internal diameter. Fiber diameter of currently available dialyzers varies between 190 and 220 μm, and fiber length between 185 and 270 mm. If fiber length is increased at constant fiber diameter and surface area, the number of fibers can be reduced. The increased length would increase shear rate and magnify the pressure drop. These 2 events have opposing effects: the increment in shear rate increases ultrafiltration, but the magnification of the pressure drop may imply that filtration equilibrium will occur before the end of the fiber. A substantial pressure drop occurs if fiber diameter is decreased. This would limit the ultrafiltration profile along the fiber and may also make

it more difficult to rinse the dialyzer free of blood at the end of the procedure. A critical minimal inner fiber diameter has been considered to be 180 μm. Fiber wall thickness varies depending on the nature of the membrane with synthetic fibers having thicker walls than cellulose-based fibers. Cellulosic membrane hollow fibers have undergone a progressive decline in thickness since their initial introduction because of their strength. This has led to an improvement in the clearance of small solutes and higher ultrafiltration rates. These features could be used to obtain high urea clearances with a smaller surface area, the latter being an important determinant of complement activation with some cellulosic membranes [3].

Blood Compartment Volume

Dialyzers have decreased in size since their initial development. This smaller size minimizes blood loss and stress on the patient's circulation. Since the late 1970's, there has been a 3-fold decrease in dialyzer weight and a 5-fold decrement in dialyzer total volume. The improvements in design and material have had a major impact on storage and cost. The blood compartment volume of currently used dialyzers varies between 18 mL in the pediatric size dialyzers and 150 mL in the largest adult dialyzers. Dialyzer blood volume is only a small fraction of the total extracorporeal circulation volume. The volume of blood in the dialysis tubing is usually larger than that in the dialyzers and varies between 160 and 270 mL. Thus, the size of the blood compartment of a dialyzer is not a critical factor in the choice of a dialyzer. However, the size of the configuration of the header and end-chamber may affect the ease of reuse and smoothness of blood flow in the dialyzer.

Blood Flow Distribution

In most hollow fiber devices, the fibers are potted in a tubular housing, which makes it easier to obtain a tight seal between the header and the housing. To assure even blood flow distribution, blood inlet and outlet are designed to allow the same blood velocity and pressure to be uniformly present in all fibers.

Dialysate Flow Distribution

Since the fibers in the bundle are not ideally spaced, and due to the nature of dialysate inlet/outlet designs, dialysate flow is not uniform over the entire membrane. At each end of the dialyzer, one can find conical sections (with the base at the end) where dialysate flow is reduced, being close to nil at the very ends of the fiber bundle. This implies that the active area for diffusion is smaller than the area for ultrafiltration. The longer a dialyzer is, the smaller the contribution of these low dialysate flow areas to the total surface of the fiber bundle. Nonuniformity of fiber arrangement can lead to dialysate channeling. One solution to the problem is to utilize separators between the fibers to optimize packing density. This can be achieved by either the use of "fins" on the outside of hollow fibers [4], or by insertion of a yarn weave prior to potting.

Housing Material

Blood comes into contact with the housing material in the inlet and outlet end caps. These are made of amorphous, rigid, and transparent material usually consisting of polystyrene, polycarbonates, or other polymers. They may be gas permeable, and polycarbonates can adsorb ethylene oxide (ETO) during the ster-

ilization process. The coloring of the end caps for inlet/outlet differentiation while useful in practical terms, interferes with the ability to examine the device at the end of the procedure for determination of the proportion of clotted fibers.

Potting

The function of potting material is to ensure a tight seal between the blood and dialysate compartments and to hold the hollow fibers. Potting material belongs to the polyurethane group which has a high affinity for ETO [5]. Further, the isocyanates used in the potting polymerization are haptens and can theoretically cause immunoallergic reactions. However, this has not been documented clinically [6].

Table 1. Membranes Used in Hollow Fiber Dialyzers

Cellulose Based
Regenerated Cellulose
Cuprophan
Saponified cellulose ester
Several varieties of regenerated cellulose
Modified Cellulose
Cellulose acetate
Cellulose diacetate
Cellulose triacetate
Synthetically modified cellulose
Hemophan
SMC
PAN-Regenerated cellulose
Synthetic Based
Hydrophilic by nature
EVAL C
EVAL D
Hydrophilic by process
Polycarbonate
PMMA
PAN (AN69,PAN-DX,SPAN)
Hydrophilic by blending
Polyamide
Polysulfone
Polyethersulfone/polyarylate (PEPA)

Membrane Materials

Dialysis membrane can be composed of one of four different materials: cellulose, substituted cellulose, cellulosynthetic, and synthetic (Table 1). The type of membranes can influence several aspects of dialyzer function including solute and water transport, sterilization methods, blood interactions, and other parameters. Cellulosic membranes remain to date the most commonly used membranes. According to the United States Renal Data Systems (USRDS) 1996 Annual Report, the distribution of dialyzer membranes used in the U.S. as of 1990/91, 64.6% of patients were dialyzed using an unmodified cellulose membrane, whereas in 1993 this figure had decreased to 41.8% [7]. Over the same time period, use of modified cellulose and synthetic membranes increased from 17.5 – 22.4% and 14.9 – 35.7%, respectively.

Cellulosic membranes are made up of a sequence of repetitive polysaccharide units containing hydroxyl groups, similar to bacterial cell walls. These membranes are highly hydrophilic and are associated with acute intradialytic leukopenia as well as complement activation. The development of substituted and synthetic membranes have resulted in membranes that are more biocompatible (see *Biocompatibility* p. 11). Substituted cellulose membranes are cellulose polymers with hydroxyl group substitutions (e.g. acetate, diacetate, and triacetate) making them more hydrophobic and more permeable to water

and larger solutes. Further development of synthetic cellulose membranes produced Hemophane, which has diethylaminoethyl (DEAE) radicals substituting 1% of the hydroxyl groups.

Synthetic membranes are non-cellulose based membranes and have decreased tensile strength compared to cellulose membranes. These synthetic polymers are grouped as "hydrophilic" (polyetherpolycarbonate) or "hydrophobic" (polyacrylonitrile-PAN, polysulfone-PS, and polymethylmacrylate-PMMA). In general the hydrophobic membranes are apolar, have low energy of interaction with water, adsorb proteins, are more porous and have high ultrafiltration coefficients.

The side group modifications on substituted/synthetic cellulosic membranes and the high adsorptive capacity of synthetic membranes leads to a decrease in the intensity of blood membrane interactions. The adsorptive property of these membranes may be a determinant of their biocompatibility (e.g. the PAN membrane can activate the complement system vigorously, but has a high adsorptive capacity for complement resulting in low net complement activation products that reach the systemic circulation).

Functional Characteristics of Hollow Fiber Dialyzers

Clearance is likely the most useful and important characteristic of a dialyzer, because it is a critical factor in determining the dialysis prescription. A wide range of clearances is available with significant overlap between dialyzer types and sizes that allows tailoring of the dialysis prescription to patient needs. The clinical importance of β_2-microglobulin removal by high-flux dialyzers remains to be confirmed by long-term studies [8].

Clearance

The definition of clearance as applied to hollow fiber dialyzers is identical to that utilized for the native kidney, namely the volume of blood completely cleared of a certain solute during a single passage through the organ or device. The calculation of clearance is similarly derived from a simple equation of mass balance: mass removed = mass at inlet – mass at outlet. Assuming a constant blood flow *(Q_b)* in the absence of significant ultrafiltration the above equation can be rewritten:

Mass removed = $Q_b[C_i] - Q_b[C_o]$ or
Mass removed = $Q_b([C_i] - [C_o])$

where *$[C_i]$* and *$[C_o]$* represent concentration of solute at inlet and outlet, respectively. Mass removed is by definition clearance times *$[C_i]$*, so the equation can be resolved into:

$$\text{Clearance} = \frac{Q_b([C_i] - [C_0]}{[C_i]}$$

Clearance can therefore be calculated from simple measurements of inlet and outlet concentrations and blood flow. Alternatively, in the case of dialysis or hemofiltration, clearance can also be calculated by measurement of actual solute removal (measurement of solute concentration in dialysate or filtrate factored by dialysate volume or flow rate). Given the variability and imprecise nature of both blood and dialysate flow rates, the actual collection of dialysate/filtrate over a defined period of time is likely the most accurate. However, for clinical purposes in HD, clearance by inlet/outlet concentrations is sufficient and is

relatively accurate for small solutes. For larger solutes, the degree of error may be more significant [9]. Clearance by the inlet/outlet methods does not distinguish between clearance into the dialysate and adsorption. This is particularly true for some middle size solutes, such as β_2-microglobulin, that are actively adsorbed by some membranes. For such solutes, measurement in dialysate underestimates clearance of the substance.

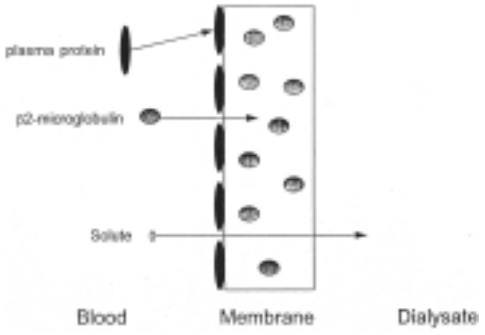

Figure 1. Model of interactions between proteins and hemodialysis membranes. Adapted from Leypoldt and Cheung, Artif. Organs 1996; 20:381-389, with permission.

Transport Mechanisms in Hemodialysis

The mechanisms of solute transport out of the blood during extracorporeal therapy are adsorption, diffusion, and convection. Although membranes have not been specifically designed for their adsorption characteristics, some membrane materials have the added benefit of removing some solutes by adsorption (e.g. β_2-microglobulin by synthetic membranes). In addition, some membranes bind activated complement factors to their surface [10] (e.g. cellulose acetate binds C3a and C5a) as well as adsorbing inhibitors for complement activation (e.g. Hemophane adsorbs factor H). Protein adsorption onto a membrane surface or within the porous structure of a dialyzer membrane can also affect solute transport.

A model proposed by Cheung and Leypoldt demonstrates how plasma proteins can interact with the membrane surface and affect the adsorption of other low molecular weight proteins and solutes (Figure 1) [11]. Binding of plasma proteins to the membrane does not result in significant changes in total protein concentration. In contrast, preferential adsorption of low molecular weight proteins (anaphylatoxins and β_2-microglobulin) can lower their plasma concentrations substantially. The pores of dialysis membranes that adsorb significant amounts of low molecular weight proteins are sufficiently large enough to permit intramembranous deposition. Presumably, these large pores also allow transmembrane transport of the low molecular weight proteins to the dialysate/ultrafiltrate compartment when the adsorption capacity of the membrane has been saturated or when the physicochemical properties of the protein do not favor its adsorption.

Diffusion across a semipermeable membrane is the primary mechanism for toxin removal by low-flux HD. The rate of diffusive transport increases with an increase in the concentration gradient across the membrane, the increase in the membrane surface area (*A*), and increase in the mass transfer coefficient (*Ko*) of the membrane times the surface area (*KoA*). Some augmentation of solute transport during HD may also occur with high rates of fluid transport (ultrafiltration) across the membrane, due to “solute drag”. Ultrafiltration adds to the clearance value, particularly for large solutes, as it is associated with further solute clearance through “convective transport” which is measured in terms of the sieving coefficient.

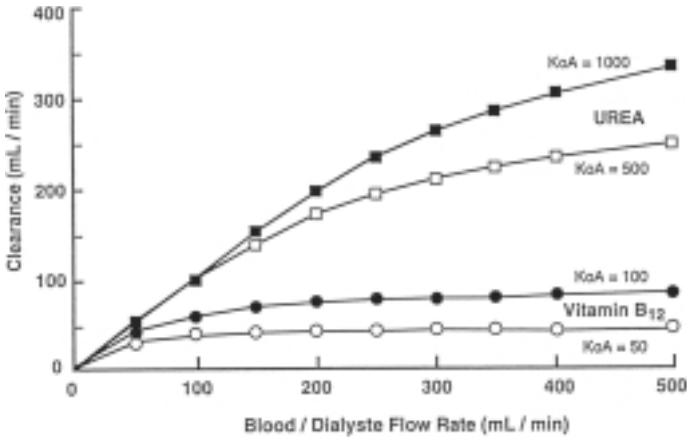

Figure 2. Dialyzer clearance of substances of different molecular weights as a function of blood/dialysate flow rate and the mass-transfer coefficient areas product (*KoA*). The clearance of large molecules (vitamin B_{12}) is not so flow-dependent as the clearance of small molecules (urea).

The sieving coefficient is the permeability of dialysis membranes to a particular solute and not its diffusability. The sieving coefficient is defined as the ratio of solute concentration in the ultrafiltrate to that of the plasma. The sieving coefficient remains near 1.0 for substances up to 1 kilodalton but is lower for larger molecular weight substances and reflect lower clearances via convection. Determination of solute sieving coefficients does not require accurate measurements of blood or dialysate flow rates. However, the sieving coefficient of a membrane may not accurately reflect its ability to remove a given solute if there is increased adsorption.

If a solute exhibits a high affinity for a membrane, it will be adsorbed with minimal transversing of the solute into the dialysate and the sieving coefficient will be low. As the membrane becomes saturated with the solute more will appear in the ultrafiltrate and there is an increase of the sieving coefficient. An example of this has been shown with β_2-microglobulin across the AN69 membrane during a hemofiltration session; this demonstrated a sieving coefficient of 0.06 that increased to 0.5 towards the end of the treatment [12].

Dialysate Flow Rates and Dialysis Efficiency

In a typical hollow fiber dialyzer blood flow and dialysate flow are arranged in a countercurrent format to allow for maximal concentration gradients between blood and dialysate at any point along the length of the fiber bundle. Flow in a concurrent direction, as may occur in error in connecting dialysate tubing, results in a 10% decrease in net solute flux. Clearance is directly related to blood flow rate within a definable range. The gain in clearance achieved by increasing flow rate is proportionally greater than that achieved by increasing dialyzer size. At low blood flow rates, for example, in continuous veno-venous hemofiltration (CVVH) and continuous veno-venous hemodialysis (CVVHD) [13] the relationship between flow and clearance has a very steep slope and approaches linearity. The dependence is lessened at the higher flow rates used in modern clinical dialysis. As evident in Figure 2, for small solutes such as urea, the clearance increases with blood and dialysate flow rate, reaching a plateau beyond which no further increase occurs with increasing flow rate. However, for a large solute such as vitamin B_{12} (surrogate middle molecule),

the plateau occurs at much lower flow rates, and clearances are relatively insensitive to flow rates above this plateau limit. It is evident therefore, that while small solutes are *"flow limited"*, large solutes are *"membrane limited"*, with the limiting clearance being related to the *KoA*.

Both blood and dialysate form an unstirred thin layer on each side of the semipermeable membrane, which solute molecules have to cross before reaching the other side of the membrane. Increasing blood or dialysate flow helps diminish these unstirred layers. With dialysate, however, the major effect of increasing flow is to improve dialysate distribution in the fiber bundle which has a greater effect than diminishing unstirred layers. Any modest gain in clearance seen with increasing dialysate flow is due to improved dialysate distribution by eliminating the channeling effect (or nonuniform distribution).

The mass transfer coefficient (*KoA*) represents the ability of a solute to pass through pores of a dialyzer (i.e. the higher this value, the more permeable the membrane). The efficiency of a dialyzer is defined by its urea *KoA*. Conventional dialyzers have a *KoA* of < 300 – 400, while high-efficiency dialyzers have a *KoA* of > 600 – 700. In clinical practice, the most effective way to increase small solute clearance is to increase blood and dialysate flow rates. For increasing large solute clearance, however, the choices are to use a more porous membrane, a membrane with a higher surface area, a thinner membrane, or some combination of these approaches to increase the *KoA*.

Ultrafiltration and Ultrafiltration Coefficient

Fluid moves under hydrostatic pressure from the blood to the dialysate compartment (ultrafiltration). The quantity of fluid ultrafiltered depends on the pressure difference between the blood and dialysate compartments. This transmembrane pressure (TMP) can be controlled by varying the pressure in the dialysate or blood compartments. Increasing negative dialysate pressure will increase ultrafiltration. The plasma oncotic pressure opposes ultrafiltration. Thus, fluid moves only when TMP exceeds the plasma oncotic pressure. The ultrafiltration coefficient (K_{Uf}) is the number of mL of fluid transferred across the membrane per hour when 1 mmHg of TMP is applied. This value varies among different membrane types, with cellulosic membranes as a group having lower K_{Uf} values than synthetic membranes. However, with the versatility of cellulose-based membranes, alterations in the manufacturing process have allowed production of cellulose hollow fibers with high K_{Uf} values suitable for all clinical uses.

The flux of a dialyzer is defined by its K_{Uf}. High-flux dialyzers have K_{Uf} ranging between 20 – 60 mL/mmHg/hour, while low-flux dialyzers have K_{Uf} < 10 mL/mm Hg/hour and medium-flux dialyzers have K_{Uf} that range between 10 – 19 mL/mmHg/hour. High efficiency dialyzers and cellulosic dialyzers have K_{Uf} of 5 – 15 mL/mmHg/hour and 3 – 5 mL/ mmHg/hour respectively. In high-flux dialyzers, as the TMP increases, a plateau is reached with no further increase in water movement due to the concentration polarization of plasma proteins on the membrane. This creates a strong oncotic pressure opposing any further increase in water movement. As pressure in the blood compartment of the dialyzer almost always exceeds oncotic pressure, there is a certain amount of obligatory ultrafiltration associated with dialysis, which may have to be replaced by intravenous fluids in the occasional normovolemic or hypovolemic patient.

The relation between ultrafiltration and K_{Uf} can be expressed as follows:
Ultrafiltration = K_{uf} × TMP × dialysis time (in hours).

For example, if the clinician wishes to remove 4 L of fluid during a 4 hour dialysis using a dialyzer with a K_{Uf} of 5, the TMP should be adjusted to 200 mmHg. This will give a total ultrafiltration of 4 L (5 × 200 × 4). In practice, due to difficulties with accurate pressure measurements and variable K_{Uf}s of the same membrane under different conditions of use, it is often difficult to predict the exact amount of fluid that will be removed by the end of dialysis. Modern dialysis machines continuously measure ultrafiltrate, thus allowing for frequent adjustments and leading to more precise fluid removal. The published K_{uf} of a dialyzer is usually determined in vitro and is often an overestimate. In vivo, the K_{uf} may be decreased due to excessive protein layering, hematocrit (HCT) concentration, or fiber clotting.

Membrane Permeability

Membranes are also classified based on membrane permeability to middle molecules. There is general correlation between high water flux and high permeability to middle molecules (i.e. high-flux dialyzers tend to remove more middle molecules than low-flux dialyzers which are relatively impermeable). The Hemodialysis (HEMO) Study sponsored by the US National Institutes of Health has proposed that the β_2-microglobulin clearance be used to define permeability of dialysis membranes to middle molecules. According to this scheme, a dialyzer with β_2-microglobulin clearance < 10 mL/min is categorized as a low-flux (permeability) dialyzer, whereas one with clearance greater than 20 mL/min is classified as a high-flux (permeability) dialyzer. For a given high-flux membrane (e.g. one with a small surface area), the *KoA* of urea may be low (i.e. low efficiency). For a given low-flux dialyzer (e.g. one with a large surface area), the urea *KoA* may be high (i.e. high efficiency). Figure 3 demonstrates the general effect of “flux” and “efficiency” on removal of solutes with a wide range of molecular weights [14].

Red Cell Effects

Unlike studies in vitro with homogenous solute solutions, blood is a heterogenous fluid and solutes in it may be subject to compartmentalization between the fluid phase and formed elements. In addition, binding of solutes to formed elements or to plasma proteins may affect the component available for free exchange across a dialyzer membrane. For small molecules that are readily diffusible such as urea, the range of error between in vitro and in vivo clearance is small, on the order of 3% for variations in HCT within the clinical range [15]. Formulas to predict this effect for various types of dialyzers have been developed [16]. For other solutes however, particularly for protein bound solutes, the differences may be more substantial [17].

The almost universal use of recombinant human erythropoietin (rHu-EPO) in ESRD patients has led to questions regarding the influence of this patient factor on dialyzer performance. Investigations of the effects of increases in HCT on the clearance of urea by hollow fiber dialyzers [18] suggest that a change in HCT would alter only the blood side resistance. The modest contribution of the latter to overall resistance implies that a major change in blood side resistance (50%) would have only a minor effect on overall

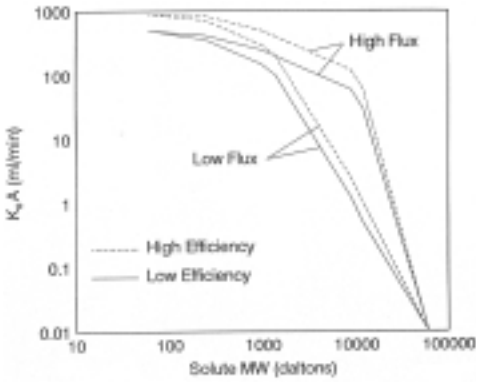

Figure 3. Theoretical *KoA* profile of high and low flux (permeability to middle molecules) dialyzers and high and low efficiency dialyzers. Adapted from Leypoldt and Cheung, Artif. Organs 1996; 20:381-389 with permission.

resistance (11%) and consequently on urea clearance (5%). For the clinically relevant range of variations in HCT (19 – 39%) there is little change in urea clearance.

Backtransport

Backtransport has been divided into backdiffusion and backfiltration [19]. The former is driven by the concentration gradient of a given substance and can occur in any dialyzer. Bicarbonate transfer from dialysate to blood is one example of therapeutic backdiffusion, whereas endotoxin transfer would represent an example of pathologic backdiffusion. Backfiltration is a convective phenomenon dependent on the presence of a pressure gradient directed from the dialysate compartment to the blood compartment. Backfiltration can occur in the setting of high-flux dialysis, as the pressure drop in the blood compartment along the fiber length dips below inlet dialysate pressure. This occurs under conditions of low TMP. Backfiltration almost never occurs under conditions of low-flux dialysis, and its occurrence during high-flux treatments depends on the transmembrane pressure used. Backfiltration is a crucial issue for device safety, because any contamination of dialysate or wash-out from the membrane can reach the blood side.

Hemofiltration and Hemodiafiltration

Hemofiltration

In hemofiltration, the ultrafiltrate flow through highly permeable membranes is augmented by increasing TMP and hydraulic permeability with absence of dialysate flow; ultrafiltration fluid losses are replaced by a substitution fluid, which is most often a modified Ringer lactate solution. The administration may take place either before (predilution) or after (postdilution) the hemofilter. Predilution requires substantially more substitution fluid than postdilution. The total volume of exchange for classic hemofiltration ranges from 20 – 40 L per treatment; the treatment typically carried out in thrice weekly sessions, each lasting 4 – 5 hours. The equipment for hemofiltration consists of the extracorporeal blood circuit, which has a geometric organization similar to that used in HD. In contrast to the complex hydraulic system required for HD, the hydraulic circuit in hemofiltration is markedly simpler.

The need for special equipment to allow hemofiltration to be performed safely, together with the high cost of replacement fluid, has limited the use of this technique to the management of acute renal failure (ARF) in critically ill patients with vascular instability.

Another major concern about hemofiltration is related to the fact that essentially large molecules are removed, and small-molecule removal is disappointing unless high volumes are ultrafiltered and substituted.

Hemodiafiltration

Hemodiafiltration combines the characteristics of conventional HD with hemofiltration, which permits increased clearance for middle and small molecules. This strategy may have a beneficial effect, not only on removal of molecules with a high molecular weight but also on removal of smaller molecules with substantial protein binding. At least for small protein-bound compounds, such as hippuric acid and indoxyl sulfate, superior removal by hemodiafiltration has been demonstrated compared to conventional HD. In contrast to hemofiltration, during hemodiafiltration only 8 – 15 L of replacement solution is used, which is infused into the venous return of the extracorporeal circuit. In general, an isotonic saline solution containing lactate as a buffer is used as a substitution fluid.

The life-sustaining aspects of HD and other deputative procedures described above should not obscure the fact that these treatments are merely an approximation of natural kidney function. None of these treatments accomplish any of the endocrine or metabolic functions of the natural kidney. Table 2 shows calculated convective solute clearances for various artificial kidney treatment techniques using the simple approximation that clearance equals the product of ultrafiltrate rate and sieving coefficient. In each of these therapies, the convective contribution to the solute clearance is only a small fraction of the weekly clearance of the normal native kidney. Finally, even though hemofiltration and hemodiafiltration with high-flux membranes permit high ultrafiltration rates and are efficient for removing β_2-microglobulin; nevertheless, albumin loss and perhaps other proteins should be taken into account when using theses procedures. Hemodiafiltration permits β_2-microglobulin removal and high *Kt/V*, and

Table 2. Convective Clearances as a Function of Ultrafiltration in L/Week as a Function of Sieving Coefficient in Various Forms of Artificial Kidney Treatment

	Therapy, UF/week				
Sieving coefficient	Low-flux HD 7L/week	High-flux HD 10L/week	HDF 30 – 60 L/week	HF 80 L/week	Native kidney 1,200 L/week
0.1	0.7	1	3 – 6	8	120
0.3	2.1	3	9 – 18	24	360
0.5	3.5	5	15 – 30	40	600
0.7	4.9	7	21 – 42	56	840
0.9	6.3	9	27 – 54	72	1,080

is probably the best way to treat chronic renal failure (CRF). Nevertheless, it is a very expensive procedure to perform in safe conditions.

Hemodialysis Membrane Biocompatibility

Blood-membrane Interactions

When blood encounters the HD membrane, several reactions are triggered including the complement cascade, the coagulation cascade, and the contact-phase pathway. In addition to these protein mediated pathways, evidence suggests that cellular mechanisms can also be activated during HD, both upon direct contact of cells with the membrane as well as by products of complement activation.

Complement Activation

During HD, complement activation proceeds via the alternate pathway. Among the different types of dialysis membranes, new cuprophane (CU) membranes activate complement to the greatest degree. The hydroxyl (OH) group on the surface of the CU membrane is thought to promote the deposition of C3b on the surface and the association of C3b with factor B (and subsequent activation of factor B by factor D) eventually resulting in formation of C3 convertase C3bBb and C5 convertase C(3b)nBb. There are several sequelae of complement activation including release of anaphylatoxins (C3a and C5a), formation of membrane attack complex (MAC), and activation of neutrophils and monocytes. C3a and C5a are potent, biologically active agents capable of producing intense vascular smooth muscle contraction, increased vascular permeability, and release of histamines from mast cells.

Although, CU membrane is a very potent activator of the alternate pathway, and has two OH groups attached to its glucan ring, substitution of 1% of these OH branches by DEAE residues (Hemophane) results in significant attenuation of complement activation. In addition, other membranes such as PAN and AN69 appear to activate complement system (locally), yet do not contain these OH moieties.

An alternate hypothesis for defining the complement activation potential of biomaterials has recently been proposed. Instead of defining an activating biomaterial as one that favors the deposition of C3b and the subsequent initiation of the positive feedback loop by C3bBb, the new hypothesis emphasizes the important inhibitory role of factor H. Thus, discrimination between activating and nonactivating biomaterial depends on the relative capacity of the surface to bind factor B or factor H. A membrane that promotes preferential binding of factor H (leading to inactivation of C3b and termination of the propagation of the complement cascade) and does not favor the binding of factor B has a low capacity to activate complement. Cellulose membranes have low affinity for factor H, an abundance of hydroxyl radicals, and little or no capacity to adsorb anaphylatoxins (C3a,C5a) and are therefore associated with the highest levels of complement activation.

Activation of complement is maximum at 15 minutes and lasts up to 90 minutes after initiation of HD with new cellulose-derived membranes. As HD proceeds, the rate of complement activation decreases. The mechanisms for this decrease have not been well-defined, but is thought to be due to coating of

the membrane with protein films [fibrin, albumin, C3 fragments, particularly C3b (covalently-bound) and C3c, C3d (non-covalently bound)]. For the same reasons, reused cellulose has a low complement activating capacity, a characteristic that may be beneficial to patients. It should be noted however, that reuse techniques which employ hypochlorite (in addition to formalin) remove the membrane coated protein, therefore abrogating the potential benefits of reuse. On the other hand, reuse with a mixture of peracetic acid/hydrogen peroxide also allows the surface of the membrane to become coated with protein which improves the membrane biocompatibility after repeated use.

Importance of Factor D

Factor D is the essential, rate-limiting enzyme of the alternate pathway of complement activation. Its molecular weight is 23 kilodaltons (kD), and its plasma concentration is increased approximately 10-fold in patients with ESRD due to impaired renal elimination. This high level of functionally active factor D is directly responsible for enhanced activation of the alternate pathway in the plasma of ESRD patients. In vitro and in vivo studies done by Pascual and colleagues using specific blocking antibodies against factor D have shown that blockade of factor D function achieves blockade of alternate pathway activation. It follows logically that adsorption of factor D on dialysis membranes could inhibit alternate pathway activation and plays an important role in the biocompatibility of PAN and PMMA membranes. In studies done by Pascual et al., there was a substantial decrease of circulating factor D in blood at the end of a HD session (80% with PAN/AN69 and 50% with PMMA, compared to less than 10% with cellulose acetate), with adsorption accounting for 98% and 85% of factor D removal by PAN and PMMA, respectively. No adsorption occurred on cellulose membranes [20].

Contact Pathway Activation

The contact pathway is activated by Hageman factor (factor XII). In particular, negatively-charged surfaces are potent activators of this pathway. PAN, with a negative charge of –153.9, induces a greater degree of activation of this pathway than the CU membranes (neutral charge). It is thought that the negative surface charge induces a conformational change of factor XII which promotes interaction between factor XII and pre-kallikrein, which is facilitated by surface-bound high molecular weight kininogen (HMWK). Once activated, kallikrein is potent in liberating bradykinin from HMWK.

Activation of Cellular Components

Neutrophils, monocytes, lymphocytes, red cells and platelets all are influenced by contact with the membrane. Activation of neutrophils leads to upregulation of adhesion receptors, release of proteinases and other intracellular enzymes, reactive oxygen species, leukotrienes, and platelet activating factor. Activation of monocytes leads to production of monokines, such as interleukin-1 (IL-1) and tumor necrosis factor (TNF).

There are many potential consequences of repeated exposure of blood cells to surfaces capable of causing activation (Figure 4). Neutrophils are sequestered in the lung and other vascular organs. In addition, the ability of neutrophils activated by the membrane to respond to a secondary stimulus is significantly abrogated, and may leave the patient more susceptible to infection. When peripheral

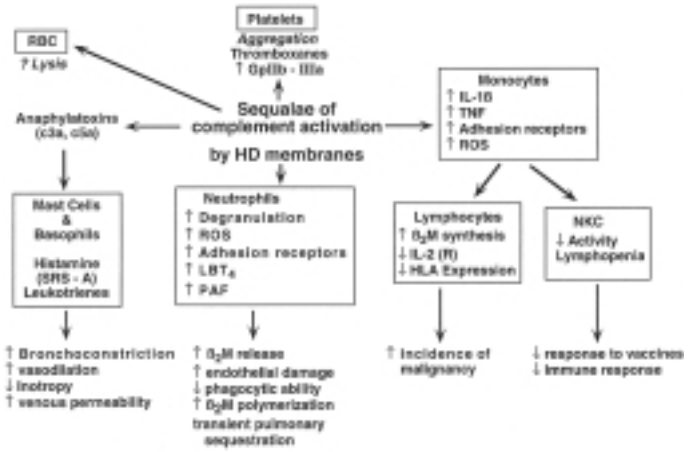

Figure 4. Sequelae of complement activation by hemodialysis membranes. (abbreviations per text details).

monocytes obtained during HD are lysed in vitro, their intracellular content of cytokines are found to be substantially elevated compared with monocytes obtained predialysis [21]. This observation suggests that peripheral monocytes are indeed activated even though they may not release their cytokines extracellularly during dialysis; these intracellular cytokines may eventually be released during the interdialytic period. These monocytes are chronically activated and have decreased ability to respond to stimuli such as endotoxin and phytohemagglutinin. Finally, the ability of peripheral blood mononuclear cells to express high-affinity IL-2 receptors, and the activity of natural killer (NK) cells have been shown to be reduced by the bioincompatibility of the membrane.

Although red blood cell (RBC) survival has been shown to be significantly reduced in dialysis patients, such a shortened survival has not been directly related to the biocompatibility of the dialysis membrane. Nevertheless, experience with the heart-lung bypass system has shown that complement activation, and specifically the release of the MAC (C5b-9) plays a major role in RBC membrane fragmentation and hemolysis.

Clinical Consequences of Bioincompatibility

The interactions of the dialysis membrane with the components of blood has the potential to lead to numerous clinical sequelae. In some areas, the evidence is supportive, but perhaps not conclusive. There are other areas in which membrane biocompatibility may play a role, but the available evidence is either based primarily on animal data or in vitro work. Areas in which the evidence is supportive include improved survival and recovery from ARF with biocompatible (BCM) compared to cellulosic bioincompatible (BICM) membranes, lower morbidity and mortality in patients on long-term HD using BCM as compared to patients dialyzed with BICM, and decreased incidence of infection, β_2-microglobulin (β_2M)-amyloid bone disease, and decreased catabolism. Areas in which potential sequelae of biocompatibility exist (but concrete human evidence is lacking) include the rate of loss of residual renal function, hypoxemia, pulmonary changes and decreased RBC survival.

Acute Reactions

"First-Use" Syndrome

A subset of patients receiving dialysis, estimated at 3 – 5% of the dialysis population, experience recurrent but less serious reactions to new CU membranes but not to their own used membranes. Reactions vary in severity, but usually consist of shortness of breath, chest tightness, back pain, as well as nausea, vomiting, and hypotension. Symptoms appear within the first 15 minutes of dialysis and are attenuated after 90 minutes. The first-use syndrome is the result of complement- mediated inflammatory processes. Patients who exhibit first-use syndrome have been shown to consistently activate complement (and therefore have very high levels of serum C3a desarginine) to a great degree in response to new cellulose membranes than do patients without this syndrome. In its most recent paper (1995), the Center for Disease Control (CDC) has determined that of all dialyzers sterilized with ETO, the cellulose based dialyzers are the ones associated with the highest frequency of first-use syndrome. The CDC also states that this association remains valid even after many of the patients who experience severe adverse first-use symptoms have been switched to gamma-ray sterilized dialyzers.

Anaphylactoid Reactions (AR) with AN69 Dialyzers

Several reports have described a high incidence of AR in patients dialyzed with high-flux membranes while simultaneously using angiotensin-converting enzyme (ACE) inhibitors. Many of these reports implicate PAN as the membrane most commonly involved in these reactions. A recent report that surveyed dialysis centers reporting AR showed that of 72 patients on a combination of ACE inhibitors but dialyzed with other membranes, and only 2 of 519 patients (0.4%) dialyzed with PAN membrane but not on ACE inhibitors developed AR. More recently, such reactions have been reported in patients on ACE inhibitors and dialyzed with PS and cellulose acetate membranes that have been re-used with Renalin.

The PAN membranes have been shown to generate high levels of bradykinin because they activate the contact-phase pathway vigorously. Kininase is an enzyme which degrades bradykinin. This enzyme is also inhibited by ACE inhibitors. The concomitant use therefore of PAN membranes and ACE inhibitors may lead to high levels of circulating bradykinins and adverse hemodynamic effects due to known physiologic effects of bradykinin (peripheral vasodilation, pulmonary airway constriction, and release of histamine from mast cells).

Acute Renal Failure (ARF)

Recently, the results of 2 prospective randomized studies have shown that the survival rate and the rate of recovery of critically ill patients from ARF were significantly higher when BCM were used compared to the use of BICM (CU). Schiffl et al. from Munich randomized 26 patients with ARF to low-flux Cuprophan membranes and another 26 patients to high-flux AN69 membranes [22]. The Cuprophan group required 35% more dialysis sessions, had longer duration before recovery from renal failure (22 days vs. 15 days), lower survival (35% vs. 62%, $p = .052$) and higher incidence of lethal sepsis (46% vs.

15%, p = .02). Hakim et al. compared 35 patients with ARF dialyzed with low-flux Cuprophan membranes with 37 patients dialyzed with low-flux PMMA membranes [23]. In patients without oliguria before the initiation of dialysis, the Cuprophan group had a higher incidence of developing oliguria (75% vs. 40%, p = .047), a lower probability of recovering from renal failure (40% vs. 85%, p = 0.003) and lower survival rate (40% vs. 80%, p = .01). However, no differences were recorded in the patients who had oliguria before the initiation of dialysis.

In a recent multicenter study comparing BCM and BICM membranes, significantly better survival and recovery from ARF with BCM patients, particularly in the patients without oliguria before initiation of dialysis was demonstrated. It was also shown that patients who recover renal function, the recovery occurred earlier in the group of patients dialyzed with biocompatible membranes. These results are of importance for critically ill patients with ARF, since the mortality rate in most series has remained around 60% despite an improvement in the general management of these patients.

Chronic Renal Failure (CRF)

There is no definitive evidence that patients on regular HD using BCM have a lower morbidity and mortality as compared to patients dialyzed with BICM. This is mainly due to the lack of well-designed, prospective and randomized studies that address these important issues. However, several non-randomized studies support the possibility that the use of BCM is associated with improvement in morbidity and mortality when compared to patients dialyzed with cellulosic membranes. Recent data from the USRDS confirms the reduction in the relative risk of mortality in long term HD patients dialyzed with non-cellulosic membranes. Hakim et al. analyzed prospective data on 2410 patients from the USRDS [24]. They found that patients dialyzed with synthetic membranes or substituted cellulosic membranes (acetate, diacetate, triacetate, and Hemophane) had approximately 25% reduction in relative risk of mortality compared with those dialyzed with regenerated (unsubstituted) cellulosic membranes, after adjustment for *Kt/V* of urea and comorbid conditions. However, this was not a randomized, controlled trial and the synthetic membranes tended to be high-flux, whereas the regenerated cellulosic membranes were low-flux.

Leypoldt et al. reanalyzed a similar subset of data from the USRDS [25]. Membranes were categorized according to their clearances of vitamin B_{12} as a marker of middle molecule removal. They found that, after adjustments for comorbidities, patient mortality correlated highly and inversely with calculated vitamin B_{12} clearance. This effect was independent of Kt/V.

Improvement in other features of dialysis treatment, such as increasing the delivered dose of dialysis or improving blood pressure control may mask or override, in part, adverse reactions to cellulosic membranes. One study from Tassin, France found that excellent patient survival can be obtained with cellulosic membranes if a higher dose of dialysis is delivered (24 hours/week, Kt/V=1.67) with an optimal control of blood pressure. This study has been cited as evidence that the type of dialysis membrane is irrelevant for clinical outcome. However, there is concern for selection bias with this study because of the exclusion of diabetic patients.

β_2-Microglobulin (β_2M)

In a large retrospective multicenter study of chronically dialyzed patients, van Ypersele de Strihou found that patients, treated with PAN/AN69 (as compared to CU membranes) had fewer radiological signs of dialysis-related amyloidosis (DRA). The difference in relative risk was clearly higher in older patients.

Although the precise mechanisms of amyloidogenesis are not completely understood, it must be noted that a "uremic concentration" of β_2M are a prerequisite for the development of DRA. It has been shown that the synthesis and release of β_2M are regulated by cytokines such as TNF, IL-2, and interferon γ and β. That BICM may increase β_2M production and accumulation in patients on regular HD is supported by studies which demonstrated an increased β_2M messenger RNA (mRNA) expression and production in lymphocytes and mononuclear cells cultured at the end of regular dialysis sessions with cellulosic membranes. Polymerization of this protein into amyloid fibrils might be enhanced by proteases and from complement-activated leukocytes. An additional factor in the propensity of patients dialyzed with cellulosic membranes to develop β_2M-amyloid bone disease may be due to the fact that most of the cellulosic membranes are low-flux membranes; these membranes do not have pore sizes large enough or an adsorptive surface to effect a significant clearance of β_2M from the circulation. On the contrary, removal of β_2M by PAN/AN69 is substantial (60% of total removal due to adsorption and 40% due to transmembrane passage). Removal of β_2M by high flux PMMA has been shown to be small and to occur mainly (more than 90%) by adsorption. Other membranes such as PS and polyamide have also been shown to possess adsorptive properties for β_2M, although less than PAN (adsorption of β_2M to PS membranes has been shown to represent < 20% of total β_2M removal, which occurs mainly by diffusion/convection). It should be noted that, although the removal of β_2M with membranes such as PAN and PMMA is important and permits a decrease of serum levels by 50% at the end of a normal dialysis session, it is still insufficient to compensate for the continued synthesis of β_2M (approximately 1500 mg/week). Nevertheless, a significant removal of β_2M during each dialysis may slow the continuous accumulation of β_2M in uremic patients. Overall, the potential benefits of synthetic membranes in preventing DRA may be predominantly related to decreased synthesis of β_2M by mononuclear cells rather than increased removal of β_2M. Equally important, these membranes by limiting repeated complement activation, cytokine production or protease release, may decrease the propensity to β_2M amyloidogenesis (β_2M polymerization or proteolysis).

Protein Catabolism and Malnutrition

Although the causes of malnutrition are multifactorial, there is increasing evidence that the use of bioincompatible membranes (BICM) contributes to malnutrition by eliciting acute catabolic effects during the dialysis procedure through vigorous activation of the complement system. The evidence of this catabolism was first shown by excess release of amino acid in normals and chronic HD patients exposed to BICM by Bergstrom and colleagues. Lindsay et al. have also shown evidence to support their proposal that for the same dose of dialysis, patients on a high-flux biocompatible membranes (BCM) had a higher protein catabolic rate (reflecting higher dietary protein intake) than patients on low-

flux BICM. Parker and Hakim have recently shown in a prospective randomized study a positive impact of the use of BCM independent of its flux characteristics on specific markers of nutrition and outcome. Recent data from the USRDS suggest an improvement in relative risk of mortality in patients using BCM compared to cellulosic membranes. The improvement was specific for infectious mortality and cardiovascular mortality, 2 causes specifically linked to malnutrition.

Infection

Uremic patients have enhanced susceptibility to infection due in part to impaired neutrophil function [26, 27]. Neutrophils eliminate bacteria through a series of carefully orchestrated events, including adherence to vascular endothelium, migration through the endothelium to the sites of infection, ingestion of bacteria, and killing the bacteria by the generation of reactive oxygen species and the release of microbial enzymes. There is increasing evidence that the HD membrane plays an important role in this enhanced susceptibility to infection [26 – 31].

One retrospective study compared the major causes of mortality in approximately 1000 patients before and after their HD membranes were changed from cellulosic to a biocompatible polysulfone membrane [32]. The most significant difference in the cause of death between these 2 time periods was in the incidence of infection, which was decreased by approximately one-half during therapy with the polysulfone membrane. Similar results were noted in another report in which the rate of hospitalization for infections in patients switched to a polysulfone membrane was one-half that in patients dialyzed with a cellulosic membrane [33].

Neutrophils from patients dialyzed with cellulosic membranes have a significantly attenuated metabolic response to phagocytic stimuli such as latex or zymosan when compared to neutrophils from patients treated with a polysulfone membrane [34]. During a follow-up of approximately 6 months, there was a higher incidence of clinically apparent infections in patients dialyzed with a BICM. Serum from patients dialyzed with BICM may inhibit the adherence ability of hematopoietic cells. As an example, one study found that serum collected from patients being dialyzed with cuprophane HD membranes significantly ameliorated the ability of granulocytes and monocytes to adhere to human saphenous vein endothelial cells [35]. No significant effect was observed with serum from patients undergoing dialysis with polysulfone HD membranes.

There is also evidence that lymphopenia and impaired natural killer (NK) cell function occur in patients dialyzed with BICM. Switching to a BCM can improve the lymphopenia [36] and NK function [30]. NK cells can spontaneously lyse target cells without prior sensitization; they are important in providing resistance to viral infection and destroying tumor cells. The impairment in NK function with cellulosic membranes may explain, in part, why HD patients have immune defects and an increased incidence of malignancy.

Dialyzer Reuse

Dialyzer reuse is the disinfection of a dialyzer for reuse by the same patient. Reuse has been utilized in chronic HD since the 1960's and has become the standard of care, albeit

amidst financial and clinical controversy. The development of reuse is the result of economic pressures from fixed reimbursement and increasing duration of dialysis therapy. The development of automated systems for reprocessing dialyzers has made the process more efficient and practical. Reuse has also provided a cost-effective means for widespread use of more expensive high flux/high efficiency dialyzers.

Epidemiology

Since 1982 there has been a steady increase in the number of centers and patients reusing dialyzers; 77% of dialysis centers and 83% of patients as of 1995 [37]. In the US, dialyzers are reused in 87% of non-hospital based dialysis units compared to 42% of hospital-based units, and in 87% of for-profit facilities compared to 56% of nonprofit units and 31% of government-owned units [38]. The average number of treatments a dialyzer can be used is approximately 13 with a maximum number of reuses around 30 [39]. The amount of financial savings by reprocessing dialyzers is substantial. With 5 manual reuses, a conservative estimate of savings has been set at $ 3,250/year per patient [40]. In the United States the estimated average savings per year with reuse is $276 million/year and a decrease in medical waste of 4,000 tons [41].

Automated vs. Manual Reprocessing

Dialyzers may be reprocessed manually or by using an automated device. Manual reprocessing is more labor intensive, results in variable quality control, and may result in fewer reuse cycles for an individual dialyzer vs. automated reprocessing. If performed meticulously, manual reuse is not associated with an increased incidence of pyrogen reactions vs. automated reprocessing [42]. Forty percent of US HD centers use manual reprocessing while the other 60% use automated equipment. Automated reprocessing devices may be single station (processing one dialyzer at a time) or multistation (multiple dialyzers simultaneously). The benefits for automated systems are:

- reproducibility of the reprocessing method,
- ability to perform dialyzer testing as a step in the reprocessing method,
- decreased risk of human error,
- assurance of the correct concentration of sterilant and adequate filling of dialyzer with germicide, and
- procedure documentation.

There are several reports that describe a decrease in the severity of first use syndrome with automated reprocessing vs. manual methods. One study with manual formaldehyde reprocessing showed 12 symptoms of first use syndrome (as described in the section on *acute reactions*), most notably for chest and back pain, were found to occur more frequently during the first use of a dialyzer than with following reuses [43]. In contrast, a separate study has shown that first use symptoms were eliminated using machine processed dialyzers. There were no differences in the incidence of symptoms between the first use of a machine processed dialyzer and subsequent reuses [44]. The differences between the incidence of first use symptoms (manual versus automated) may be explained by the following observations. New dialyzers contain particulate fibers of up to 1 mm in length, plasticizers leached from polyvinylchloride used in the manufacturing of dialyzer casing, and Limulus Amebocyte Lysate-reactive ma-

terial (LAL-RM) [45, 46]. No adverse clinical reactions have been attributed to intravascular delivery of particulates in dialysis patients, but plasticizers have been associated with cutaneous necrotizing vasculitis and hepatitis [45]. The reduction of symptoms during first use and subsequent reuse may be attributable to more rigorous pretreatment with machine processing (vs. manual) and the removal of particulate matter contained in the "dry pack" dialyzer.

Dialyzer Reprocessing

The steps involved in dialyzer reprocessing are summarized in Table 3 and briefly outlined below.

Table 3. Steps in Dialyzer Reprocessing

Assurance of AAMI water quality
Rinsing: Reverse ultrafiltration
Cleaning: Bleach vs. hydrogen peroxide
– Pressure leak testing
Performance Testing
– Total cell volume
– Clearance studies
– in vitro *Kuf*
Disinfection/Sterilization: Use of one of the following methods
– Formaldehyde
– Peracetic acid based germicides (e.g. Renalin)
– Glutaraldehyde
– Heat disinfection
Storage
Preparation for the next dialysis

Water Quality

When the recommended practice guidelines of the Association for Advancement of Medical Instrumentation (AAMI standards) for dialyzer reuse are followed carefully, disinfection of dialyzers or multiple use by the same patient is relatively safe and effective in eliminating infection, pyrogen reactions, and other potential complications associated with germicide use. Preparation of high quality water according to AAMI guidelines for the preparation of dialysate and filtration of dialysate can reduce the presence of bacteria and endotoxin by 99.9%. Water used to prepare disinfectional solutions should have a bacterial colony count of < 200 bacteria/mL and/or a bacterial LPS of < 1 ng/mL [47]. Bacteria and endotoxin contamination of water used to dilute disinfectant solution is one of the most common measures by which reuse related sepsis and pyrogenic reactions may occur.

Cleaning the Dialyzer (Bleach vs. Hydrogen Peroxide)

After reverse ultrafiltration of the dialyzer the next step in processing is cleaning the membrane. Sodium hypochlorite (bleach) diluted to ≤1% reduces the biocompatibility of BICM due to removal of coated proteins. There is also an increase in protein permeability of polysulfone dialyzers with repetitive bleach processing (see later section on increased protein loss with reuse). Hydrogen peroxide is another method for cleaning dialyzers. The use of hydrogen peroxide does not remove coated proteins so BICM become biocompatible with continued reuse but at the expense of ultrafiltering capacity.

Dialyzers that undergo cleaning with bleach can result in direct membrane damage. Pressure-leak testing is recommended to detect acquired membrane defects. A pressure gradient is produced by running pressurized air or nitrogen (at a pressure 20% above the maximal operating pressure) into the blood side of

the dialyzer or by subjecting the dialysate compartment to a negative pressure of 250 mmHg over 30 seconds [42]. A pressure change of < 0.83 mmHg/second indicates preserved membrane integrity. A pressure change < 1.25 mmHg/second for high-flux membranes is acceptable for continued membrane reuse.

Performance Testing

Total Cell Volume (TCV)

Dialyzers that are reused have decreased solute transport. This results from the number of occluded fibers, thickening of the dialyzer membrane, membrane pore occlusion and decreased membrane permeability. Monitoring of the TCV of a hollow fiber dialyzer provides a single method of detecting decreased solute clearance for a single dialyzer. The TCV is the volume of aqueous liquid needed to fully prime the blood compartment of a hollow fiber dialyzer. The TCV includes the fiber bundle volume and the dialyzer header volume. Measurement of TCV consists of an air or nitrogen rinse of the blood compartment using a compressible bulb with measurement of the amount of displaced liquid. Dialyzers having a TCV of < 80% of the original measured volume should not be reused. A TCV of < 80% represents an estimated decrease in urea clearance of approximately 10% [48].

Clearance Studies

In vitro urea, sodium chloride and B_{12} clearances may be determined for reused dialyzers. These measurements afford a more accurate means of assessing dialyzer clearance than TCV [42]. Protein and lipid components in blood, the level of the hematocrit, and incomplete red cell to serum equilibration of some substances during a single passage through the dialyzer blood compartment may reduce dialyzer clearance in vivo. In vitro clearances overestimate actual in vivo clearance. Clearance studies are not routinely performed on all dialyzers, but on a sampling basis, once yearly. A 10% loss of clearance in a reprocessed dialyzer is regarded as acceptable [42].

In Vitro Ultrafiltration Coefficient (K_{uf})

The K_{uf} of a dialysis membrane is the number of mL of fluid/hour that will be transferred across the membrane/mmHg pressure gradient across the membrane. The permeability of a dialyzer membrane to water is measured by determining the number of milliliters of water per minute (Q_f) passing through the membrane at a given pressure and temperature. Changes in the K_{uf} reflect changes in membrane surface area (occluded fibers) and membrane resistance (protein coating). The in vitro K_{uf} falls much less rapidly than the TCV because thrombosed fibers may still have high in vitro hydraulic permeability. This method may therefore overestimate the in vivo clearance of reused dialyzers, and close attention must be paid to expected and actual weight losses in the patient. Dialyzers are discarded when Q_f falls below 75% of the initial value [42].

Disinfection/Sterilization

Germicides

Disinfectant is run into the blood and dialysate compartments of the dialyzer, and the

dialyzer is capped and stored in a bag or container for 24 hours. Disinfectants currently used in reuse are formaldehyde, peracetic/acetic acid/peroxide mixture (Renalin), and glutaraldehyde. Formaldehyde was the most common germicide in use with manual reprocessing until the late 1980's. The advent of automated techniques and concerns regarding the toxicity of formaldehyde and potential injury to patient and staff has lead to increasing popularity of Renalin. In 1995, 57.5% of U.S. dialysis facilities were using Renalin, 37.9% were using formaldehyde, and 3.5% were using glutaraldehyde.

All germicides used in the reprocessing of dialyzers are biophysical hazards and have been implicated in clinical complications. Formaldehyde is the oxidation product of methanol and is rapidly oxidized in the body to formic acid and can be measured in normal human blood at a concentration of 2.5 parts per million (ppm) [49]. It is irritating to the eyes and airways in small concentrations of 0.1 – 5 ppm, causing tearing, coughing, and burning. Glutaraldehyde is 3 times more toxic than formaldehyde, with toxicity occurring in the range of 0.04 ppm. Peracetic acid or peracetic acid mixture (Renalin) has little vapor toxicity, but can cause skin burning on contact. In concentrated form it is chemically stable, but when diluted to clinical use concentrations it is less stable and requires monitoring to guarantee its germicidal effectiveness [50].

There is no standardization of the germicidal concentrations in dialyzer reuse. Formaldehyde concentrations vary from 0.5 – 4%, but it is most commonly used in the 2.0 – 2.5% range. When formaldehyde is used to disinfect dialyzers at room temperature, it should be used at a concentration of 4%, because this has been shown to be required for the effective killing of nontuberculous mycobacteria [51]. Renalin has been shown to be an effective disinfecting agent at 0.5% peracetic acid, but is most commonly used at the 3 – 3.5% concentration [50]. Renalin has been shown to be more effective in killing Bacillus subtilis and nontuberculous mycobacteria than 4% formaldehyde, which has resulted in gradually increased use by most dialysis centers.

Heat Disinfection

As an alternative to chemical (germicide) disinfections, heat disinfection has been developed for use with Fresenius polysulfone membranes in 1991. Heat disinfection has proven safe for patients and staff, easy to use, and environmentally friendly. All infecting agents, including spores, are destroyed by dialyzer reprocessing with heated water (100 – 105° C) for 20 hours. However, these temperatures may result in structural damage to the dialyzer, limiting reuse. Dialyzer reprocessing by using 1.5% citric acid heated to 95° C for 20 hours is an alternative method that produces equivalent microbiologic effects [52, 53]. Five years of experience at one center with heat at 95° C and 1.5% citric acid was associated with no pyrogen reactions or positive dialyzer blood cultures. Dialyzer performance as measured by kinetic *Kt/V* and measured urea clearance do not show significant changes with heat disinfection. In another center's experience, both small and large molecule clearances and the sieving coefficient for protein were insignificantly altered by the process. Whereas the procedure is relatively simple, quality assurance indicators are essential. This combination of heat and citric acid has proven to be safe and efficacious for disinfection with the number of reuses increased to 12 – 15, equal to the national average for other germicidal disinfection.

Advantages and Disadvantages of Reuse

Table 4. Advantages and Disadvantages of Reuse

Advantages
- Decreased intradialytic symptoms
- Decreased first use syndrome
- Increased biocompatibility
- Increased use of high-flux/efficiency dialyzers
- Decreased exposure to LAL-RM with first use of a dialyzer

Disadvantages
- Environmental exposure to chemical disinfectants
- Increased risk of clinical infections
- Pyrogenic reactions
- Infusion of sterilants and germicides: anti-N-AB formation/vascular irritation
- Decreased dialysis delivery: alteration of dialysis membrane integrity
- Increased protein loss/variation in β_2 micro globulin clearance

Decreased Intradialytic Symptoms

There is an overall reduction in the incidence of intradialytic symptoms in patients using new vs. reprocessed dialyzers. In a randomized double-blind crossover study comparing reprocessing with formaldehyde vs. patients using new dialyzers, there was a greater incidence of back and chest pain in patients using new dialyzers, whereas there was a lower but not statistically significant reduction of cramps, shortness of breath, nausea, vomiting, and nervousness in patients using reused dialyzers [54]. Another study has shown a reduction in the incidence of fever, sweating, respiratory distress, chest pain, nausea, vomiting, and hypotension in patients transferred from a unit practicing single use to a unit using formaldehyde reprocessed dialyzers [55]. More studies have been conducted using the more prevalent peracetic acid-hydrogen peroxide based germicides. One study reported fewer intradialytic symptoms using dialyzers reprocessed with peracetic acid when compared to formaldehyde [56]. Another prospective study has shown no difference in the intradialytic symptoms and changes in blood pressure between patients using new dialyzers compared to patients using automated-machine reprocessed dialyzers with peracetic acid-hydrogen peroxide based germicide [57].

Decreased First Use Syndrome and Improved Biocompatibility

Reprocessing of cellulosic dialyzers with formaldehyde, peracetic acid and glutaraldehyde results in improved biocompatibility of the dialyzer. Improved biocompatibility is thought to be related to the deposition of albumin, complement and fibrin on the blood compartment surface of the dialyzer. Protein residues coat hydroxyl ions of cellulosic membranes [58] and isolate the membrane surface from subsequent blood-membrane interactions. With reprocessing, C3b is firmly bound to the membrane and prevents further activation of the complement cascade [59]. This reduces the sequelae of complement activation, such as leukopenia due to pulmonary sequestration of leukocytes with resultant hypoxemia [60]. Activation of the kinin system, thromboxane production, histamine release and the production of various cytokines [61] may also contribute to the clinical syndrome of dialyzer bioincompatibility. Dialyzer bioincompatibility is restored with the use of bleach in the reprocessing process at high

concentrations (> 4%) due to membrane surface protein degradation. However, when lower concentrations are used (1%) with formaldehyde, biocompatibility is retained [62].

First use reactions (as described above in *Clinical Consequences of Bioincompatibility: Acute Reactions*, p. 14) are greatly reduced in patients using reprocessed cellulose dialyzers. When biocompatible membranes (e.g. cellulose acetate or synthetic membranes) are used for dialysis, there may not be a reduction in first use symptoms with reuse [63, 64].

Increased Risk of Clinical Infection

Dialyzer reuse has been associated with localized outbreaks of bacteremia and nontuberculous mycobacteria in centers where dialyzers are reprocessed. Most infections are a result of suboptimal concentrations of sterilant, such as the use of < 4% formaldehyde and inadequate mixing of Renalin [37]. Gram negative bacteria that occur naturally in water *(Pseudomonas, Flavobacterium, Acinetobacter, Alcaligenes, Xanthomonas, Serratia, Achromobacter, Aeromonas)* grow rapidly to levels of $10^3 – 10^6$/mL of water prepared by reverse osmosis, deionization, and carbon filtration. Contributing factors in the development of gram negative bacteremia are:

- suboptimal concentration of sterilant,
- inadequate mixing of germicide after dilution,
- variation in germicide concentration with manual reprocessing, and
- cross contamination of dialyzers by bacteria on technicians gloves. Another source of contamination is the replacement of inadequately disinfected headers and O-rings after these surfaces are removed for cleaning of residual blood products [65].

Highly resistant strains of non-tuberculous mycobacteria *(Mycobacterium chelonae, M. fortuitum, M. gordonae, M. scrofulaceum, M. avium, M. abscessus, M. intracellularis)* may survive and grow in processed and domestic water supplies. *Mycobacterium chelonae* has been found by a CDC survey to exist in the water supply of 83% of 115 surveyed centers and 50% of all water samples were positive for this organism [66]. These mycobacteria have been associated with outbreaks of septicemia and death in some reuse centers [67, 68]. Use of 4% formaldehyde is effective in killing nontuberculous mycobacterial as are carefully controlled solutions of peracetic acid and glutaraldehyde [37].

Increased Protein Loss/Variation in β_2-Microglobulin (β_2M)Clearance

Increased dialyzer membrane permeability can develop in some dialyzers undergoing repeated bleach reprocessing. This increase in permeability leads to increased losses of albumin and smaller proteins such as β_2-M. Protein sieving after the use of bleach as a cleaning agent and formaldehyde disinfection of polysulfone membranes was reported in 1995 [69]. Total protein and albumin losses were measured by total dialysate collection from 1 – 25 uses and compared with dialyzers processed without bleach for 8 – 25 uses. This study found that total protein losses were relatively small during the first 10 uses (1.5 – 3.6 mg/dL), but increased significantly after 15 – 25 uses (7.9 – 19.9 mg/dL). When multiplied by the total dialysate volume of 83 L, this represented protein loss of up to 20 g per dialysis. Albumin losses showed a similar increase up to 14.4 mg/dL after 23 – 25 uses. Dialyzers processed without bleach for similar numbers of uses had protein losses of 1.4

– 2.7 mg/dL and no measurable albumin. After removal of bleach from the reuse procedure, serum albumin concentration in the patients increased from 3.55 – 3.79 g/dL for the 6-month period before and after the change in the reuse procedure, respectively. In contrast to these findings, others have shown that in reused polysulfone dialyzers repeatedly exposed to bleach/formaldehyde reprocessing, albumin and protein losses into the dialysate were of smaller magnitudes; average albumin losses were 0.5 – 1.0 g during the 15th reuse [70]. In addition, others have detected, in the case of polysulfone dialyzers reprocessed with bleach, only minimal protein loss into the dialysate, in the order of 1 – 2 g per dialysis over 20 reuses. No loss or only a negligible loss was detected if the dialyzer had been reprocessed with peracetic acid or heat [71].

The effect of reuse on β_2M clearance is dependent not only on the type of reprocessing method but also the number of reuses and the membrane material used [72]. β_2M clearance by most currently available, first use, low-flux dialyzers is negligible (mostly < 5 mL/min) and does not change significantly with reuse. In contrast, β_2M clearance by first use, high-flux dialyzers of either cellulosic or synthetic origin can be substantial (often > 20 mL/min) [72]. Reprocessing without bleach does not sufficiently restore the membrane surface to its original state; the secondary membrane layer formed by the adsorbed plasma proteins tends to diminish the β_2M clearance of some membranes. In reprocessing methods employing the use of bleach solutions, the concentration of the bleach used and the time of exposure dictate the permeability of the membrane to β_2M and other proteins. Studies of polysulfone membranes using bleach reprocessing have shown that β_2M clearance remains constant or increases linearly. Increased β_2M clearance was determined in part due to the greater number of times a dialyzer was reprocessed (> 10) [73]. In contrast to polysulfone membranes, reuse with bleach does not alter β2M clearance of cellulose triacetate membranes [73].

Mortality and Reuse

The issue of mortality and reuse is a topic of continuous analytical research and clinical debate. The dictum of lower mortality rates seen in patients dialyzed with reprocessed dialyzers has been changed by 2 recent national studies [74, 75]. Both studies show, via different analytical methods, a higher risk of mortality with use of peracetic acid-based disinfectants in free-standing dialysis units. The original database for both studies consisted of 53,634 dialysis patients from 673 free-standing centers using reused, low-flux dialyzers, and 12,463 patients dialyzed in 184 free-standing centers using only single-use, low-flux dialyzers. In the first study [74] patients were followed for one year and the mortality rate was recorded. The results were as follows:

- patients in centers reusing dialyzers treated with glutaraldehyde had a 17% higher mortality than did patients in centers that did not reuse dialyzers,
- patients in centers reusing dialyzers disinfected with a mixture of peracetic acid, hydrogen peroxide and acetic acid experienced a 13% higher mortality than did patients in centers that did not reuse dialyzers, and
- patients in centers reusing dialyzers reprocessed with formaldehyde as the germicide had a mortality rate comparable to that of patients in centers that did not reuse dialyzers.

In the second study [75] incident rather than prevalent end stage renal failure (ESRF) pa-

tients were followed for 4 – 5 years. Neither of these studies were randomized and potential confounding variables were not considered.

In contrast to these results, data obtained from hospital-based outpatient dialysis centers showed that the mortality associated with reuse using any one of the three germicides (formaldehyde, glutaraldehyde, and peracetic acid) was not higher than that associated with single use. One theory to explain the difference between hospital based and free-standing units is that there is greater variation in adherence to AAMI practice guidelines in free-standing facilities than in hospital-based units.

Outcome results for dialysis units reusing high-flux dialyzers have been inconclusive because a comparable control group of units not reusing such dialyzers is not available. Compared with units that employ only single-use, low-flux dialyzers, the mortality risk for patients from reusing high-flux dialyzers has been favorable [74]. How to interpret these results is difficult given the major differences between these two modalities of dialysis.

Water Treatment

Recent technological advances in dialysis practices including high flux and high-efficiency dialysis, ever-increasing dialyzer reuse, and bicarbonate dialysate have heightened awareness about the safety of dialysis water. Fortunately, the aforementioned dialysis practices have been paralleled by continuous advancement in reverse osmosis membrane technology. Reverse osmosis membranes represent an effective barrier to endotoxin and bacteria with clear benefits over simple deionization.

Essential Components of Water Purification

The efficiency of a water purification system depends on the capacity of the system, the nature of the incoming water supply, seasonal variations in municipal water quality, and the desired quality of the water product. Table 5 lists the components, advantages, risks, and AAMI recommendations for users of HD water treatment systems. Fluoride contamination is reviewed by Mujais and Ismail in the chapter on “Complications During Hemodialysis”.

Chloramines and Carbon Filtration

Most adverse events related to a chemical toxin in the water supply are due to chloramines. Chloramines can pass readily through dialysis membrane and cause oxidant damage to red blood cells (RBC’s) (hemolysis). Most episodes of chloramine toxicity stem from ever-changing nature of municipal water supplies. Water can contain naturally-occurring organic substances, such as humic acid, that react with chlorine to form trihalomethanes. Trihalomethanes are carcinogenic, and in 1979 the Environmental Protection Agency (EPA) ruled that their level in drinking water supplies should not exceed 0.1 mg/L [76]. Chloramines are an effective alternative to chlorine since they are more stable and maintain bactericidal activity at lower total chlorine concentrations. Removal of chloramines from water can be achieved only by carbon adsorption or the addition of ascorbic acid to

Table 5. Components, Advantages, Risks, and AAMI Recommendations for Users of Hemodialysis Water Treatment Systems

Component	Advantages	Bacterial proliferation (Other risk)	AAMI recommendations
Sediment filters	Removes particulate matter	+	Opaque housings Pressure gauges, pre and post filters Monitor pressure drop (ΔP) Change filters when $\Delta P > 10$ psi Monitor for bacteria
Water softener	(1) Removes calcium and magnesium (2) Protects against scaling of RO system	+	Automatic regeneration with "bypass" Use pellet salt designed for softeners Check timer before dialysis Check hardness before dialysis
Carbon filters	Absorbs chlorine and chloramine	+	Use disposable carbon (GAC) Use 2 GAC tanks in series Each GAC tank with EBCT of 3-5 min 5μ filters downstream Monitor for exhaustion; replace exhausted tanks (backup system replaces spent tank when chloramine level > 0.1 mg/L) Monitor for bacteria
Reverse osmosis	(1) Rejects univalent and divalent ions (2) Filters bacteria	+	Must produce AAMI quality water Audible/visual alarms Monitor salt passage (2 × initial) (Salt passage = 100-rejection rate) Monitor pretreatment
Deionization	Removes all types of cations and anions	+	Continuously monitor resistivity (< 1 mΩ/cm) Temperature compensated monitor Visual and audible alarm GAC upstream Don't use industrial or process resin
Disinfection	Prevention of endotoxemia and pyrogenic reactions	Anti-N-like antibody formation (formaldehyde) Anaphylactoid reactions (ACE inhibitor/Renalin/reprocessing)	4% formaldehyde, 24 hours contact time 1-2% formaldehyde, 40°C, 24 hours Renalin/diacide

GAC: granular activated carbon GAC; EBCT: empty bed contact time; maximum mesh size 12 × 40 and minimum iodine number of 900; ACE: angiotensin-converting enzyme; RO: reverse osmosis

the water [77]. These processes have a finite capacity for chlorine removal due to variation in the source of the carbon and due to fluctuations of the chloramine concentration in the public water supply.

Granular activated carbon (GAC) will absorb chlorine, chloramines, and other organic substances from water. Since carbon filters are highly porous with a high affinity for organic material, they can be contaminated with bacteria if they are not serviced properly or exchanged frequently. The size of an activated carbon bed requires an understanding of empty bed contact time (EBCT). The EBCT is calculated as

EBCT = [V] [7.48 (gallons/cu. ft.)]/Q, where V = volume of carbon required in cubic feet, Q = water flow rate (gallons/minute).

The recommended EBCT for chlorine removal is 6 minutes and, for chloramine removal is 10 minutes.

The FDA recommends that 2 tanks filled with GAC be used in series. Each tank should have an EBCT of 3 – 5 minutes. When the first GAC filter has a chloramine concentration in the effluent filter > 0.1 mg/L, it should be replaced within 72 hours. Similarly, if the chloramine level in the effluent of the second tank exceeds 0.1 mg/L, the water must not be used for dialysis.

Aluminum Toxicity and Reverse Osmosis

In the early 1970's, aluminum toxicity was first described by Alfrey and colleagues in Denver [78]. This syndrome was characterized by speech abnormalities, myoclonus, personality changes, seizures, and progression to death within a few months [78]. Extensive studies revealed that patients with the syndrome had high levels of aluminum in organs such as the brain and bones [79, 80]. Further investigation revealed that the syndrome occurred in areas with high aluminum in the municipal water and that the increased body burden could be accounted for by transfer of aluminum from the dialysate to the blood [81, 82].

Aluminum is commonly added to municipal water supplies as a flocculating agent. In aqueous solution, aluminum exists in cationic form at acidic pH and in anionic form at alkalemic pH; at neutral pH it is present mainly as colloidal aluminum [83]. Due to its chemical properties aluminum is poorly removed by softeners and ion exchange at neutral pH. The development of reverse osmosis in the 1970's provided for a mechanism of water purification and aluminum removal from dialysate.

Reverse osmosis applies the principles of high hydrostatic pressure across a semipermeable membrane to a solution to prepare a purified solvent. This process rejects 90 – 95% of univalent ions (e.g. Na^+), and 95 – 99% of divalent ions, as well as microbiologic contaminants. Accordingly, 2 – 10% of the dissolved ions will pass through the membrane into the product dialysate water. Aluminum is well rejected by reverse osmosis membranes over a wide pH range and is the method of choice for water purification. Reverse osmosis generally produces water that is safe for dialysis, but, in some instances, the quantity of dissolved salts in the dialysate water may exceed maximum safety concentrations. Reverse osmosis membrane technology advanced greatly in the late 1970's with the development of thin film composite membranes which offered several advantages over celluloid acetate and polyamide membranes. The thin film composite membranes were more resilient to frequent cleaning and/or sanitization with stronger chemical agents.

The finished water quality is thus, higher in terms of total dissolved solid rejections.

When a reverse osmosis device is used as a pretreatment to deionization it serves primarily as an economic device to provide longer service life for the deionization system. Subsequent deionization of permeate (product) reverse osmosis water is usually unnecessary.

Microbiology of Hemodialysis Systems

The primary microbial contaminants of dialysis fluids are naturally-occurring water bacteria. These include gram-negative bacteria and non-tuberculous mycobacteria (see *Increased Risk of Clinical Infection* p. 24 above). These bacteria can survive and multiply in water containing little organic matter, such as deionization or reverse osmosis treated water. Disinfection strategies for HD systems are targeted at gram-negative bacteria. Although bacteria may be inactivated by exposure to chemical germicides, bacterial endotoxin may remain in the HD system. Endotoxins are produced by bacteria and can persist despite the absence of bacteria. Although non-tuberculous mycobacteria do not produce endotoxins, they are, compared to gram-negative bacteria, more resistant to chemical germicides and have been responsible for patient infections as a result of inadequately disinfected dialyzers.

AAMI Standards for Hemodialysis Water Quality

Water treatment is a vital aspect of HD in which knowledge and technical skills are of utmost importance. Each component of a water treatment system brings with it its own risks and requirements for safe and proper use as well as for monitoring and surveillance. A summary of the AAMI's recommendations (1993) for safe and proper water treatment and the use of water treatment system components is listed in Table 6.

Disinfection strategies for dialyzer reprocessing are quite different from those targeted to the water supply. While low-level disinfection is adequate for water treatment systems components, high-level disinfection is mandatory for dialyzer reprocessing. Water monitoring for reprocessing hemodialyzers therefore requires more stringent criteria. While there are no AAMI standards for endotoxin levels in water used to prepare dialysate, water for rinsing, reprocessing, and disinfecting dialyzers should contain less than 5 endotoxin units/mL (1 ng/mL).

The recognition that non-tuberculous mycobacteria can be resistant to certain germicides and still cause infection spurred the establishment of current safety microbiologic standards for dialyzer reprocessing. After reverse ultrafiltration and cleaning with bleach $< 1\%$; or hydrogen peroxide $\leq 3\%$ and peracetic acid $\leq 2\%$, manual or automated pressure tests for leaks should be performed. Dialyzers should then undergo disinfection/sterilization. Germicides are generally instilled into the blood and dialysate compartments and remain in contact for ≥ 24 hours. The 3 most commonly used agents are 4% formaldehyde, peracetic acid-hydrogen peroxide-acetic acid mixture (Renalin) and glutaraldehyde (Diacide). A 2% formaldehyde solution should not be used because some mycobacteria can survive in 2% formaldehyde at room temperature. However, even 1% solutions of formaldehyde may have excellent germicidal efficacy when dialyzers are incubated at 40° C for 24 hours.

Table 6. AAMI Hemodialysis Water Quality Standards*

Microbiologic and Endotoxin Standards for Dialysis Fluids

Type of Fluid	Microbial count (CFU/mL)[a]	Endotoxin (EU/mL)[b]
Water to prepare dialysate	≤ 200	No standard
Dialysate	≤ 2000	No standard
Water to rinse and reprocess dialyzers	≤ 200	≤ 5[c]
Water to prepare dialyzer disinfectant	< 200	≤ 5[c]

Chemical Contaminants Monitoring

Contaminant	*Suggested Maximum Level (mg/L)*
Calcium	2 (0.1 mEq/L)
Magnesium	4 (0.3 mEq/L)
Sodium	70 (3 mEq/L)
Potassium	8 (0.2 mEq/L)
Fluoride	0.2
Chlorine	0.5
Chloramines	0.1
Nitrates	2
Sulfate	100
Copper, Barium, Zinc	0.1 each
Aluminum	0.01
Arsenic, Lead, Silver	0.005 each
Cadmium	0.001
Chromium	0.014
Selenium	0.09
Mercury	0.002

*Association for the Advancement of Medical Instrumentation, American National Standards, Inc. AAMI Standard and Recommended Practices. Vol. 3: Dialysis 1993, Arlington, VA.
[a]CFU = colony-forming units; [b]EU = endotoxin units; [c]5 EU = 1 ng.

Hemodialysis Anticoagulation

For the majority of HD patients, systemic heparinization is usually used. Variations in heparin dosage for HD, which are common, cannot necessarily be judged by body weight. The patient should have heparin requirements assessed according to a series of whole blood activating clotting times (WBACTs) or whole blood activated partial thromboplastin time (WBAPTT) determinations; each HD unit must set up its own standards for WBACTs according to the reagent and system used. For

patients at high risk for bleeding, "tight" heparin, heparin-free dialysis, or citrate anticoagulation is used.

Systemic Heparinization

Heparin is administered either by the infusion pump method or by the bolus method. A bolus dose of heparin, usually 50 U/kg of lean body weight, is given and then an infusion pump is started, delivering approximately 500 – 1,000 U of heparin/hour. The loading dose is increased to 75 U/kg if the patient is receiving recombinant human erythropoietin (rHu-EPO). The infusion pump is usually stopped 30 – 60 minutes before the end of dialysis. The WBACT is monitored and aimed at about an 80 percent increase from baseline WBACT value during heparin administration. WBACT should be performed on each new admission and then once per month:

- before dialysis,
- 1 hour after initiation of dialysis, and
- half an hour before the end of dialysis.

Towards the end of dialysis, WBACTs in the range of 170 seconds are appropriate.

Patients with external shunts or cuffed catheters should have the WBACT kept at 3.5 to 4 minutes during dialysis.

Tight Heparinization

Indications for tight heparinization include moderate bleeding risks such as pericarditis or recent surgery. Target clotting times are 150 – 160 seconds with the WBACT method. To avoid fluctuations in heparin levels, the continuous infusion technique rather than the bolus method is recommended.

Dialysis Without Anticoagulation

This is the method used in patients with active bleeding or in whom heparin is contraindicated or in patients who are high risk for bleeding. This regimen uses initial rinsing of the extracorporeal circuit with saline and heparin, but without infusing this saline into the patient. After initiation of dialysis, periodic saline rinse with 300 mL every 15 minutes is needed. This technique is not recommended with subclavian or femoral catheters or patients in whom a blood flow of at least 300 mL per minute cannot be achieved. The risk of clotting of the dialyzer is about 15% with this regimen. Blood products or hyperalimentation lipids should not be administered during heparin-free dialysis.

Citrate Anticoagulation

Citrate anticoagulation is the method of choice for patients at high risk for bleeding or who are actively bleeding. In this technique, blood in the extracorporeal circuit is anticoagulated by chelating its calcium with sodium citrate and by using a zero-calcium dialysate bath. At the same time, an infusion of calcium chloride is given to the patient through the venous limb distal to the dialyzer. Approximately two-thirds of the citrate returns to the patient and is metabolized (approximately one-third of the citrate is dialyzed). Risk of clotting with citrate anticoagulation is low, and the advantage of this method over heparin-free dialysis is that high blood flows are not necessary. Serum calcium should be monitored and risk of alkalemia should be considered since citrate is also metabolized to bicarbonate. The citrate infusion rate is adjusted according to WBACT (measured in arterial line, downstream from citrate infusion, and aimed at 100% prolongation).

Regional Heparinization

In regional heparinization, protamine sulfate is used distal to the dialyzer to neutralize the heparin administered proximal to the dialyzer. A "heparin rebound" phenomenon may occur after regional heparinization from 2 – 4 hours after cessation of dialysis and persists for up to 10 hours, possibly causing hemorrhage. This technique is rarely used at present.

Alternative Methods of Anticoagulation for Hemodialysis

Heparin Coating of Hemophan

A method of priming the dialysis membrane with heparin before HD has been introduced and used successfully in high risk intensive care unit settings, as well as outpatients. This method is based on the idea that Hemophan dialysis membranes have a high affinity for binding heparin, and that the bound heparin exerts a localized antithrombotic effect without systemic anticoagulation [84]. Gretz [85 – 87] in Mannheim, Germany, compared Hemophan to polyacrylonitrile and polysulfone and reported less activation of coagulative pathways with Hemophan. A recent study by Mujais and Chimeh [84] performed sequential doses of heparin preloading consisting of 12,000 U, 16,000 U, and 20,000 U. Twelve patients were assigned in a random fashion to undergo 3 dialysis treatments with Hemophan dialyzers and preloading using the 3 different doses of heparin. It was determined that the optimal performance of this method requires the use of 20,000 U of heparin. They also compared the performance of the Hemophan dialysis with a 20,000 U prerinse to the use of saline flushing with cellulose acetate and polysulfone dialyzers. Minimal loss of clearance (at time 15 minutes and 3 hours of dialysis) was obtained with cellulose acetate and Hemophan (< 4%) and slightly larger loss of 6% was seen with the polysulfone dialyzer.

The method of heparin preloading was performed as follows. The arterial and venous ports were connected to a 1 L bag of 0.9% saline containing 20,000 U of heparin and the circuit is run at a 200 mL/min flow rate and 10 mL/min ultrafiltration rate for 20 minutes of recirculation time. At the end of the recirculation period, the pump is stopped, the arterial port is connected to a new 1 L bag of normal saline, and the circuit is flushed with 500 mL of saline with the effluent discarded. The lines are then connected to the patient, and dialysis is started in the usual fashion. This regimen is expected to allow for > 90% of the heparin dose to bind to the membrane. Unbound heparin is flushed out of the system by the heparin-free saline rinse.

Low Molecular Weight Heparin (LMWH) Anticoagulation

LMWH have recently been recommended as an alternative to unfractionated heparin for chronic HD patients [88 – 90]. Their most important advantage over unfractionated heparin is their prolonged half-life [91], enabling single bolus administration at the start of dialysis [89, 90]. Moreover, LMWH may have a more favorable hemorrhagic to antithrombotic profile than unfractionated heparin, since they interfere less with platelet aggregation [92, 93] and vascular permeability [94]. No bleeding complications occurred during a 12-month study in which 70 stable chronic HD patients were randomized to either unfractionated heparin or LMWH. With a target hemoglobin level of 6.5 g/dL, 19 patients on LMWH required transfusions of

76 packed RBC units, which was significantly less per dialysis/filtration session than 16 patients on unfractionated heparin, who required 88 units [95].

LMWH anticoagulation with nadroparin calcium [96] is performed as follows: nadroparin calcium [25,000 anti-factor Xa Institut Choay Units (anti-XaICU)/mL, Fraxiparine, Sanofi Winthrop, Maassluis, The Netherlands] is administered intravenously as a bolus at the start of dialysis session. The dose per kg dry body weight is adapted to the HCT and to the duration of the dialysis session:

Session ≤ 4 hours
HCT < 0.30: 150 anti-Xa ICU/kg = 60 IU/kg
HCT > 0.30: 200 anti-Xa ICU/kg = 80 IU/kg

Session > 4 hours
200 anti-Xa ICU/kg = 80 IU/kg

If the dialysis session lasts > 5 hours, 2/3 of the dose is given at the start of the session and 1/3 after 2.5 hours. The maximum dose to be given pending clot formation in the extracorporeal circuit is 350 anti-Xa ICU/kg.

Dialysate Composition

Dialysate Glucose

Contemporary dialysis fluids range from glucose-free to isoglycemia (5 – 5.5 mmol/L [90 – 100 mg/dL]) or slightly hyperglycemic (5.5 – 11.0 mol/L [100 – 200 mg/dL]). Most non-insulin dependent patients tolerate dialysis with glucose-free dialysate without ill-effects despite losing 25 – 30 g of glucose across the dialyzer. A few studies, however, have shown that this glucose loss may adversely affect intermediary metabolism of carbohydrates and proteins. The adverse effects of glucose-free dialysate include a reduction in plasma glucose, a corresponding decrease in plasma insulin levels, and a marked decrease in lactate and pyruvate levels. Although these biochemical measures often are sufficient to maintain serum glucose in the physiologic range, hypoglycemia may develop during the use of glucose-free dialysate, especially in the presence of cachexia, sepsis, diabetes mellitus, or drugs such as aspirin or propranolol. Available data at present also indicate that dialysate glucose does not play a significant role in determining total cholesterol levels in non-insulin dependent HD patients.

Dialysate Buffer

Bicarbonate dialysis is considered the dialytic treatment of choice in critically ill patients, conferring many benefits over acetate dialysis in these patients including a lower incidence of arterial hypotension, less hypoxemia, and improved left ventricular stroke volume. The mechanisms by which acetate buffer results in hemodynamic instability include direct vasodilation, stimulating the release of IL-1, a vasodilatory compound, and arterial hypoxemia which results from the transfer of CO_2 across the dialysis membrane, from blood to dialysate, with consequent reflex hypoventilation. Finally, acetate dialysate may have a myocardial depressant effect.Bicarbonate dialysis is the dialysate buffer of choice and confers advantages in critically ill patients. In chronic stable HD patients, patients who are unable to metabolize acetate well: elderly patients, patients with reduced muscle mass, malnourished patients and possibly, females, tolerate bicarbonate dialysate better. These patients may be par-

ticularly intolerant to acetate with the use of high-flux dialysis, because of the high influx of acetate with these dialyzers.

Dialysate Calcium

Because dialysate calcium equilibrates with the diffusable (ionized) fraction of calcium in the plasma, a dialysate calcium of 2.5 mEq/L is equivalent to serum calcium of 10 mg/dL. The use of a high dialysate calcium (3.5 mEq/L) or low dialysate calcium (≤ 2.5 mEq/L) entails separate advantages and risks. Numerous studies have shown a beneficial effect of high dialysate calcium on the indices of metabolic bone disease as well as a reduction in parathyroid hormone (PTH) levels. High-dialysate calcium has been shown to improve hemodynamic stability during dialysis by augmenting stroke volume and cardiac output. One of the complications of high dialysate calcium is the development of hypercalcemia with concurrent use of calcium-based phosphate binders and oral or intravenous 1,25 dihydroxy vitamin D_3. In a hemodynamically stable patient, and particularly those prone to hypercalcemia during treatment with vitamin D and calcium salts, a dialysate calcium concentration of 2.5 mEq/L is recommended.

Dialysate Potassium

Low dialysate potassium can precipitate ventricular ectopy. This is most pronounced in patients with left ventricular hypertrophy, impaired left ventricular function, or in patients taking digoxin. Therefore, for patients at risk for dysrhythmias, the use of dialysate potassium < 2 mEq/L should be avoided.

Dialysate Sodium and Variation Programs

With the refinement of HD technology, variable sodium profiles during dialysis are now possible. Three different profiles have been described (as depicted in Figure 1, chapter on "Complications During Hemodialysis").

A recent study compared steady dialysate sodium of 140 mEq/L to linear sodium ramping (155 to 140 mEq/L) or stepwise ramping (sodium 155 mEq/L for 3 hours and 140 mEq/L for 1 hour) [97]. There was no major difference between the 2 ramping protocols, but compared with standard dialysis, both decreased total number of hypotensive episodes as well as that of cramping during dialysis. Between dialysis treatments, however, patients complained of more fatigue and thirst. Interdialytic weight gain following ramping was 5.1% of body weight (compared to 4.4% without ramping). Blood pressure also increased following ramping, from 143/79 mmHg to 152/81 mmHg. Even though this study indicates that most patients will have more problems between dialysis sessions when ramped, some patients (22%) do derive great benefits, with a dramatic decrease in hypotension and cramps, which will be worth the tradeoff for postdialysis complications. Interestingly, in another study comparing dialysate sodium to 140 mEq/L to a programmed exponential decrease of dialysate sodium from 155 mEq/L to 135 mEq/L which was held constant for the final half hour of dialysis, 63% of the treated hypertensive subjects were able to stop or reduce their medications on the variable-sodium program [98]. Other investigators, however, have not found any hemodynamic advantage for sodium-gradient compared to a fixed high-sodium dialysate of 140 – 145 mEq/L. In these patients, sodium-

gradient dialysis may offer its greatest benefits in 2 clinical situations:

– the initial dialysis session for a patient with advanced renal insufficiency and an extremely elevated urea concentration (> 200 mg/dL), in which case sodium modeling might decrease the risk of dialysis disequilibrium syndrome; and

– patients with a low urea mass transfer coefficient, who exhibit a delay in equilibration between intracellular and extracellular fluid compartments. In these patients, sodium-gradient dialysis may allow for more balanced urea and volume transfer.

Summary

Transport and biocompatibility characteristics are 2 important considerations when choosing HD membranes. Because of concerns about middle molecule transport and biocompatibility, the original cellophane membrane has been gradually replaced by modified cellulosic membrane and synthetic membranes for clinical use. Because of large economic benefits, dialyzer re-use has become an integral part of chronic HD in the U.S. and in some European countries. When the recommended practice guidelines by the AAMI are carefully followed, dialyzer re-use is relatively safe. The development of disinfectant methods using heat or heat and 1.5% citric acid is a promising for polysulfone membranes. Finally, the life-sustaining aspects of HD with its dramatic reversal of uremic toxicity should not obscure the fact that HD is, at best, an approximation of natural kidney function and improper clinical application of HD technology can severely compromise its therapeutic adequacy.

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