



A Clinical Update on Dialyzer Membranes

State-of-the-Art Considerations for Optimal Care in Hemodialysis

- › Key features of high performance membrane dialyzers
- › Influence of design and chemical composition on membrane performance
- › Influence of membrane characteristics on clinical status
- › Consideration of membrane features as part of the hemodialysis prescription



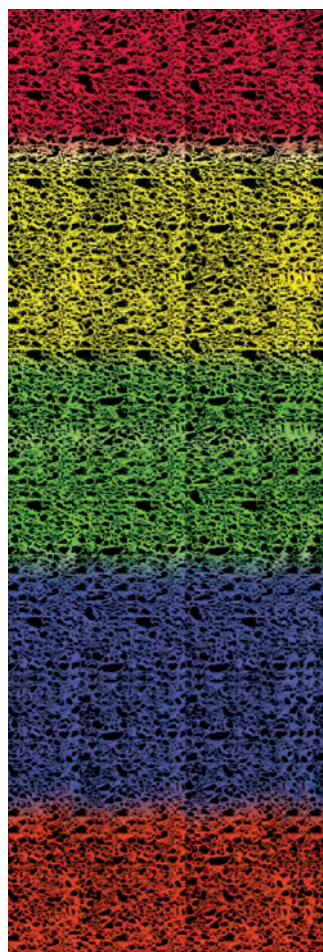
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INTRODUCTION

Membrane performance, as determined by the effectiveness of solute clearance and biocompatibility, is of greatest concern when choosing a dialyzer.¹ Technological advances in membrane design, chemical composition, and sterilization methods have led to enhanced performance and versatility to the extent that dialyzer choice may reduce morbidity and prolong survival. Accordingly, the Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Recommendation for Dialyzer Membranes and Reuse states that though the selection of dialyzer membranes and reuse practices are not included in the prescription of small-solute clearance, they can be important determinants of patient survival and quality of life.²



THIS BULLETIN

This bulletin addresses key features of dialyzer membranes, particularly high performance membranes, and how they can optimize hemodialysis treatments. Many of the membranes discussed, however, can also be employed for other renal replacement therapies such as hemodiafiltration, or for other applications such as removal of free light chains. In addition to membranes, other dialyzer features are briefly reviewed as part of the overall consideration in dialyzer selection.

HIGH PERFORMANCE MEMBRANES

High performance membrane (HPM) is a classification used in Japan to identify hollow fiber dialyzers with an advanced level of performance. The criteria for HPM include excellent biocompatibility, effective clearance of target solutes, and, pore size larger than conventional hemodialysis (HD) membranes, thus promoting the removal of protein-bound uremic toxins, and middle to large molecular-weight solutes, including β_2 -microglobulin (β_2 -M). HPM should also have a high molecular weight cut-off, a sharp cut-off curve, and a greater capacity for adsorption than

conventional HD membranes. The Japanese Society of Dialysis Therapy (JSDT) also recommends that the pore size in HPM be large enough to allow slight losses of albumin, at a rate of < 3 g/session with a blood flow rate of 200 ml/min and a dialysate flow rate of 500 ml/min.³ A larger pore size approximates the glomerular filtration of uremic toxins and albumin in the human kidney, while some protein leakage may enhance albumin turnover.^{3,4,5} Table 1 includes examples of high performance membrane dialyzers.

TABLE 1. EXAMPLES OF HIGH PERFORMANCE DIALYZERS⁶

MATERIAL	ABBREVIATION	MANUFACTURER	MEMBRANE TYPE
Cellulose triacetate	CTA	Nipro	hollow fiber
Polysulfone	PSf	Asahi Kasei Kuraray Medical	hollow fiber
		Fresenius	hollow fiber
		Toray	hollow fiber
Polyethersulfone	PES	Nipro	hollow fiber
		Membrana	hollow fiber
Polymethylmethacrylate	PMMA	Toray	hollow fiber
Polyester polymer alloy	PEPA	Nikkiso	hollow fiber
Ethylene vinyl alcohol copolymer	EVAL	Asahi Kasei Kuraray Medical	hollow fiber
Polyacrylonitrile	PAN	Gambro	hollow fiber laminated

Adapted from Saito A, Kawanishi H, Yamashita AC, Mineshima M, eds. In: *High-Performance Membrane Dialyzers. Contributions to Nephrology. Vol 173. Basel: Karger;2011.*

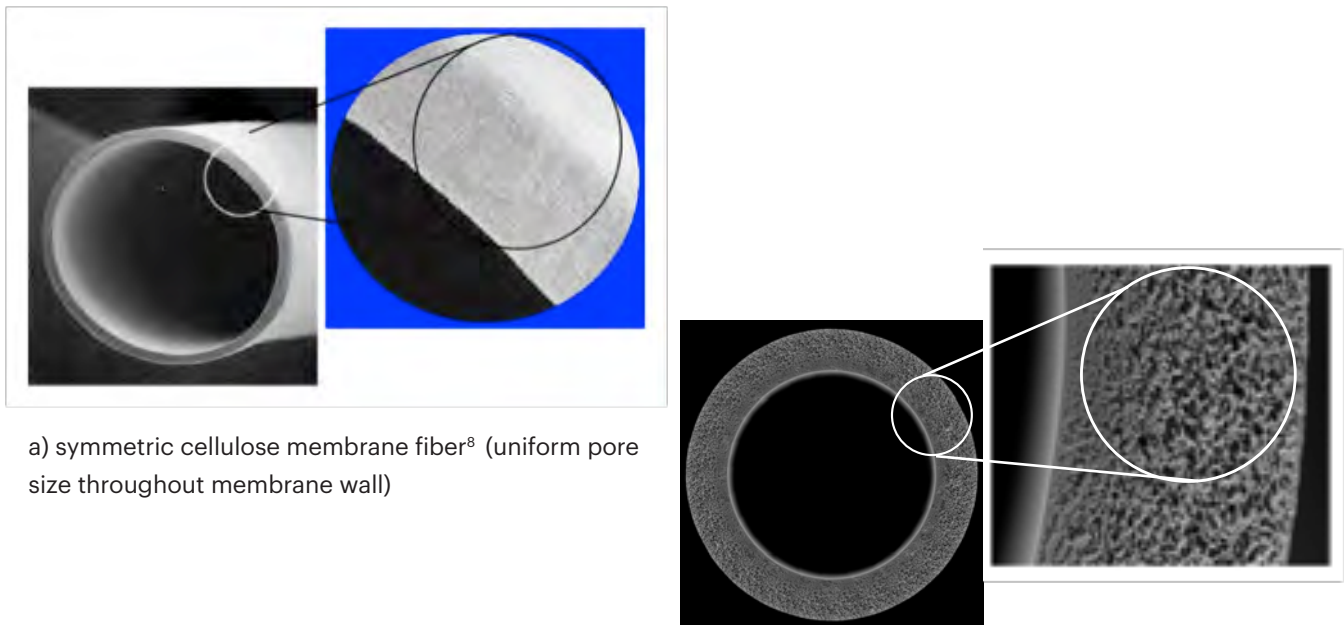


INFLUENCE OF DESIGN AND CHEMICAL COMPOSITION ON MEMBRANE PERFORMANCE

Membrane fibers are either symmetric or asymmetric, as noted in cross sectional views. (Figure 3) Symmetric membranes, which can be derived either from cellulose or entirely from synthetic polymers, have a homogeneous configuration throughout the membrane wall, with both the inner and outer layers usually containing similar pore sizes. Asymmetric membranes, however, are derived from synthetic polymers only, and have a thin inner

selective layer and an outer thick support layer; almost all membranes made of polysulfone (PSf) or polyethersulfone (PES) have this type of structure. Diffusive resistance to small molecules due to the fiber wall being thick can be compensated for by increasing porosity within the support layer. Membranes made of polyethersulfone/PVP/polyamide (PEPA) contain three layers, with the outer layer providing mechanical stability.⁷

FIGURE 3. CROSS SECTIONS OF DIFFERENT HOLLOW FIBERS^{8,9}



a) symmetric cellulose membrane fiber⁸ (uniform pore size throughout membrane wall)

b) asymmetric polyethersulfone membrane fiber⁹ (pores are larger on dialysate side of membrane wall)

Whereas cellulose derived fibers are naturally wave-like (Moire effect), synthetic fibers may be crimped to produce a rippled pattern that more evenly distributes the flow of dialysate.^{10,11} (Figure 4) Such a design prevents contact or excess packing among fibers and thus allows for better matching of blood and dialysate flows across all sections of the fiber bundle.^{10,12,13}

After the membrane fibers are secured within the potting material, they are opened by cutting them in a manner that produces a smooth and flat surface, which is crucial for preventing hemolysis, blood clotting, or retention of residual blood.⁷ (Figure 5)

FIGURE 4: RIPPLED VERSUS STRAIGHT HOLLOW FIBERS ⁹

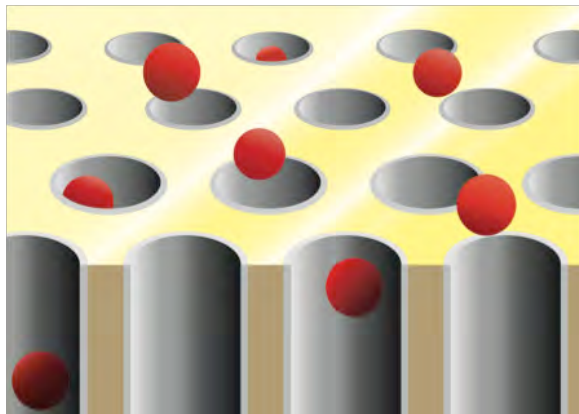


a) undulated fibers that promote even dialysate flow

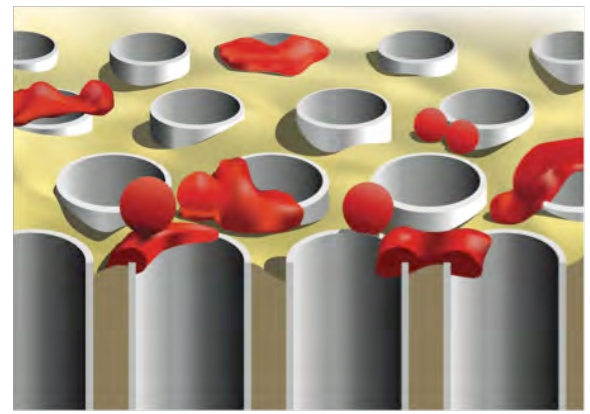


b) straight fibers

FIGURE 5. SMOOTH VERSUS ROUGH CUT BLOOD-CONTACTING SURFACES ⁹



a) smooth cut blood-contacting surface



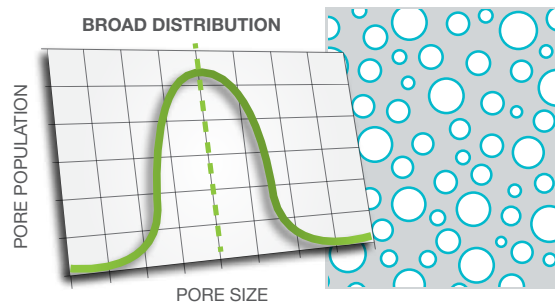
b) rough cut blood-contacting surface not



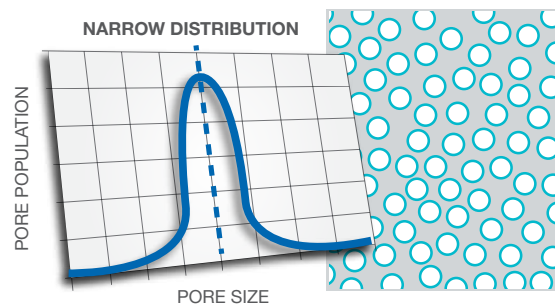
Each membrane has a molecular weight cut-off for the largest molecule that can pass through it. Knowing this parameter allows nephrologists some specificity in the ability to more effectively remove solutes of particular concern in an individual patient. Dialyzers have molecular weight cut-offs ranging from 3,000 Da to more than 15,000 Da.^{14,15} The new generation of super high-flux membranes have cut-offs closer to 65,000 Da.¹⁶

Nanotechnology has improved the uniformity of pore size, in contrast to earlier membranes that had a wide range of pore sizes, with fewer large pores produced, and thus limited removal of middle molecular weight uremic toxins.¹⁰ Membranes with a homogeneous pore size and a narrow pore size distribution have a sharper cut-off in the sieving coefficient,¹⁷ thus leading to improved passage of low molecular weight proteins while reducing the loss of albumin.^{6,18,19} (Figure 6)

FIGURE 6. PORE SIZE DISTRIBUTION AND SIEVING COEFFICIENT CUT-OFF ⁹



Non-uniform pore size and spacing on membrane surface provides reduced performance.



Optimized highly uniform pore size and distribution offers better performance.

The materials most commonly used to make hollow fiber membranes include PSf, PES, cellulose triacetate (CTA), polymethylmethacrylate (PMMA), PEPA, ethylene vinyl alcohol copolymers (EVAL), and polyacrylonitrile (PAN).⁶ The use of poorly biocompatible, unmodified cellulose dialyzer membranes is discouraged.² Accordingly, most dialyzer membranes are made from synthetic polymers, 93% of which are derived from the parent polyarylsulfone family, with 71% produced as PSf and 22% produced as PES. All membranes discussed are HPM and confer specific attributes that may be considered in dialyzer selection.²⁰ Membranes in the new super high-flux dialyzers are primarily PSf and PES.²¹

PSF MEMBRANES have the capacity to remove a broad range of uremic toxins, effectively retain endotoxins, and, provide intrinsic biocompatibility and low cytotoxicity. In addition to its higher sieving capability, increased hydraulic permeability promotes efficient transport through solvent drag (convection). Although PSf may be the primary polymer, it is blended with other polymers to give each membrane its specific attributes, as in the case of adding the hydrophilizing agent polyvinylpyrrolidone (PVP). Significant differences among PSf membranes exist because of variations in both the relative amounts of co-polymers used in a particular blend, and the fiber spinning process employed.²⁰

A new generation of **PES MEMBRANES** has been developed through an advanced fiber spinning process that creates larger, uniformly sized, and densely distributed pores. This configuration improves perm-

selectivity by creating a steeper sieving curve for low molecular weight proteins and a sharp cut-off. PES membranes are therefore known for achieving outstanding middle molecule removal with minimal albumin loss, and both their biocompatibility and endotoxin retaining characteristics adhere to the highest standards. Previously, a much higher albumin loss was required to achieve a comparable HD treatment efficacy when using dialysis membranes with inferior permselectivity. These membranes are a blend of hydrophobic base polymers, which favorably determine biocompatibility, while hydrophilic components improve transmembrane solute passage.²²

CTA MEMBRANES have a high solute permeability that can remove β_2 -M by diffusion. Their diffusive efficiency is very high because their fibers are thin and have a Moire structure, causing the flow distribution of the dialysate to be uniform. Their reported clinical benefits include high antithrombogenicity, improvement in lipid metabolism, and the reduction of biomarkers such as homocysteine and advanced glycation end products.²³ Proteomic analysis of CTA membranes has shown high adsorption of albumin, and since the adhesion of thrombocytes to a surface tends to be decreased by albumin adsorption, this would suggest that CTA may offer the potential for a lower activation of the coagulation cascade than PSf membranes, as demonstrated in other studies.²⁴

PMMA MEMBRANES have highly adsorptive properties, which may be attributed to a homogeneous structure in which the entire membrane contributes to adsorptive removal, rather than removal through only one membrane layer.^{25,26} PMMA membranes were found to reduce indoxyl sulphate, p-cresyl sulphate, and 3-carboxy-4-methyl-5-propyl-2-furanpropionic acid (CMPF), which are associated with cardiovascular damage from endothelial dysfunction and reactive oxygen species (ROS) production. Accordingly, a protein-leaking (super-flux) PMMA membrane was found to reduce serum levels of CMPF with improvements in anemia, and to reduce plasma homocysteine, pentosidine and inflammatory cytokines.²⁵ PMMA membranes have been shown to adsorb intact PTH and to improve pruritis,²⁷ enhance the response to the hepatitis B vaccine,²⁸ and to preserve muscle mass, especially in the elderly.²⁹

PEPA MEMBRANES are a combination of PES and polyarylate and have a unique structure: three layers comprise the entire inner surface skin layer; a porous layer lies within the membrane; and, another skin layer covers the outer surface. The permeability of water and solutes is controlled by the skin layer on the inner surface and the outer skin layer can block endotoxin from the dialysate side; thus it can be used as an endotoxin filter. The amount of albumin loss or β_2 -M removal can be controlled by the amount of PVP added. Versions made without PVP have resulted in minimal activation in complement C3a and C5a.³⁰

EVAL MEMBRANES are hydrophilic and uncharged, with a smooth surface that retains water, so they adsorb few plasma proteins and interact weakly with cell components in the blood.^{31,32} Therefore, there is minimal platelet activation, and little production of ROS and pro-inflammatory cytokines such as interleukin-6 and monocyte chemo-attractant protein (MCP-1) which may help patients maintain better peripheral circulation.^{33,34} Accordingly, the long-term use of an EVAL membrane may reduce oxidative stress and inflammation, and thus help reduce the symptoms of vascular disease.^{31,32}

PAN MEMBRANES are hydrophilic, so they attract water to form a hydrogel structure that confers high diffusive and hydraulic permeability. The highly specific adsorptive properties are limited on the surface, but favored within the membrane structure and with high specificity for basic, medium-sized proteins. PAN displays high permeability to fluid and a broad spectrum of uremic toxins combined with excellent biocompatibility.³⁵ Removal of MCP-1 can only be achieved through specific adsorption which has been demonstrated in a PAN membrane.³⁶

Some membranes are coated with polyethylene glycol or vitamin E in order to decrease the activation and migration of monocytes and granulocytes, thus improving biocompatibility.^{7,37} Such membranes have been found useful in reducing hypotension during HD. Synthetic membrane surface modifications with heparin have also been developed for heparin-free dialysis for those with increased risk of bleeding.³⁸



PERFORMANCE CONSIDERATIONS FOR SELECTING A DIALYZER

SOLUTE REMOVAL

Solute removal in hemodialysis occurs through a combination of diffusion, convection, and adsorption. The uremic solutes removed by hemodialysis are divided into three main categories (Table 2): 1) small water-soluble compounds such as urea with an upper molecular weight of < 500 Da that can be removed with any dialysis membrane by diffusion, 2) the larger middle molecular weight molecules (500 – 15,000 Da) which can only be removed through dialyzer membranes with enhanced transport capacity and large enough pores (high flux), and 3) protein-bound molecules, mostly with a molecular weight of 500 Da, but larger and more difficult to remove because of being bound to proteins.²⁷

TABLE 2. CATEGORIZATION OF SMALL, MIDDLE, AND LARGE MOLECULES ¹⁴

CLASSIFICATION OF SOLUTES	MOLECULAR WEIGHT RANGE (DALTONS)
Small molecules urea (60), creatinine (113), phosphate (134)	<500
Middle molecules vitamin B12 (1355), vancomycin (1448), insulin (5200), endotoxin fragments (1000-15000), Parathromone (9425), β_2 -microglobulin (11818)	500-15000
Large molecules myoglobin (17000), Retinol-Binding Protein (RBP) (21000), EPO (34000), albumin (66000), Transferrin (9000)	>15000

Adapted from Azar AT, Canaud B. Chapter 8: Hemodialysis system. In:

Azar T, ed. Modelling and Control of Dialysis Systems. SCI 404. Berlin: Springer-Verlag; 2013.

The efficiency of solute clearance through diffusion is expressed as K_oA for a particular dialyzer and a given solute, where K_o is the mass transfer coefficient and A is membrane surface area. K_oA values for urea are provided by dialyzer manufacturers, but if those values are determined in vitro, then they should be reduced by approximately 20% to better replicate in vivo membrane exposure to blood. The manufacturer's in vitro data must not be used in urea kinetics to determine the dialysis prescription.^{14,17}

Convective separation of solutes and low molecular weight proteins from large serum proteins and blood elements is achieved with high flux dialyzers through increased porosity and efficiency of mass transfer.³⁹

Adsorption is the adhesion of macromolecules and proteins to the membrane surface without penetration, and it primarily depends upon the internal pore structure and the hydrophobicity of the membrane.²⁵ A highly adsorptive membrane may also have negative consequences by reducing the diffusive and convective capacities. Therefore, a moderate level of protein adsorption combined with the ability to bind protein-bound uremic toxins appears to be recommended features in a membrane.²⁷

Clearance may be considered the most important characteristic of a dialyzer because it is a critical factor in determining the dialysis prescription. Urea clearance is the most commonly used measure, since it is used to calculate the dialysis dose. Phosphate clearance and uric acid clearances are not always reported but can be helpful when treating significantly high phosphate or uric acid levels. But because phosphate is an intracellular ion, using a dialyzer with a high phosphate clearance can cause the plasma value to decrease rapidly without a major impact on its total removal.¹⁴

Enlarging membrane pore size beyond that of conventional low-flux dialyzers has led to increased β_2 -M clearance, and because it is easy to measure, β_2 -M is now considered a surrogate marker for middle molecular weight solutes. The membrane sieving coefficient for β_2 -M has gained acceptance by both dialyzer manufacturers and the medical community to assess membrane flux.^{14,40}

Dialyzers are considered high-flux if their ultrafiltration coefficient (K_{uf}) is > 15 ml/h/mmHg and their ability to clear β_2 -M > 20 ml/min.¹⁶ In Japan, however, the classification of dialyzers refers to five types, from I to V, based on the clearance of β_2 -M of less than 10, 30, 50, 70, and more than 70 ml/min, respectively, at a blood flow rate of 200 ml/min and a dialysate flow rate of 500 ml/min. Types IV and V are considered to be super high-flux dialyzers, with molecular weight cut-offs closer to that of the human kidney (65,000 Da), thus allowing for efficient removal of middle and large size uremic toxins, and greater clearance of inflammatory cytokines than conventional high-flux membranes.^{16,41}

A Cochrane review based upon 3820 patients with end stage renal disease, from all available RCTs, could not determine overall efficacy and safety of high-flux compared with low-flux HD, but did conclude that high-flux HD may reduce cardiovascular mortality by about 15% in people requiring HD.⁴² In the Hemodialysis (HEMO) study, high-flux HD provided significantly lower rates for cardiac and cerebrovascular mortality after 3.7 years on HD, as compared with low-flux HD.^{43,44,45} In the Membrane Permeability Outcome (MPO) study, high-flux HD provided higher survival rates for patients with serum albumin ≤ 4 g/dl, improved survival for diabetics, and even for low-risk patients, as compared with low-flux HD.^{46,47}

Aside from research findings, one should consider that backfiltration almost never occurs in low flux dialysis, and its occurrence during high flux treatments depends on the transmembrane pressure used. This is a crucial safety concern because any contamination of dialysate or wash-out from the membrane can reach the blood side. Forward and backfiltration coefficients are different in vitro and even more so in vivo because of the protein layer in the blood compartment and the structure of the membrane.^{14,48} Additionally, correcting an interdialytic weight gain of more than 5 kg within a dialysis session of less than 3 hours with high flux dialysis could lead to a significant increase in the risk for hypotension, especially in patients with poor cardiac function or autonomic neuropathy.¹⁴



BIOCOMPATIBILITY

Complement Activation

The level of complement activation produced by a membrane is considered a significant determinant of membrane biocompatibility. All membranes activate complement and leukocytes to some extent, but unmodified cellulose membranes are known to be the most potent activators, and are therefore considered bioincompatible. Complement activation products include anaphylatoxins such as C3a, which may cause allergic reactions during dialysis, and can also lead to acute intradialytic pulmonary hypertension, chronic low-grade systemic inflammation, and leukocyte dysfunction.¹⁷

Platelet Activation

A significant amount of platelet activation can occur during hemodialysis and cause thrombosis in the dialyzer. Plasma fibrinogen binds to the membrane, causing platelet adhesion and activation, while blood flow within the dialyzer and the extent to which air can be removed from it during priming can both impact clotting, regardless of the membrane's chemical composition.^{48,49} Recently, cases of thrombocytopenia have been reported with PSf membranes that have been sterilized by electron beam radiation, though the mechanism is unclear.^{50,51}

Toxins

The chemical composition of other dialyzer components such as the housing also influences biocompatibility. Bisphenol A (BPA) in dialyzers has been the focus of investigation by the Food and Drug Administration because it has been eluted from dialyzer housing made of polycarbonate.⁵² BPA and phthalates have been found to leach into the blood during dialysis,^{53,54} and this is superimposed on blood levels that are already elevated because BPA excretion is reduced in renal disease.⁵⁵ Patients receiving dialysis with PSf membranes have displayed elevated BPA levels after treatment,^{56,57} and thus some manufacturers have developed dialyzers that contain no BPA. Similarly, the FDA has reported that di (2-ethylhexyl) phthalate (DEHP) may pose a health risk in medical devices such as dialyzers, and therefore some manufacturers have removed it from their products.^{52,58}

The potting material, which secures the hollow fibers at both ends of the dialyzer, is made of polyurethane, which has a high affinity for the sterilizing agent ethylene oxide (ETO). When ETO accumulates in the potting material, it can diffuse into the blood and cause anaphylactic reactions.^{59,60} The dialyzer housing is made of polycarbonates or other polymers that may be gas permeable and thus adsorb ETO during sterilization.⁵⁹ The use of ETO is now less common, having been replaced with steam and gamma radiation.⁷

INCORPORATING DIALYZER CHOICE INTO THE HEMODIALYSIS PRESCRIPTION

As described by Daugirdas, many excellent nephrologists follow an empiric model when devising the hemodialysis prescription and place patients on the largest dialyzer that they can afford, and dialyze them for the longest amount of time that the patient will agree to and with the highest blood flow rate that the vascular access will accommodate. They then check the URR and/or Kt/V, and if deficient, attempt some corrective action. Alternatively, he suggests using basic principles of kinetic modeling while incorporating any needed adjustments to improve clearance, such as extending treatment time, increasing dialysate flow rate, increasing blood flow rate, or moving to a larger dialyzer.⁶¹

Studies and guidelines point to the benefits of synthetic high-flux membranes, but individual patient needs should be factored into dialyzer selection. Along with performance parameters, it is the clinician's challenge to find the optimal dialyzer based on the patient's size, years on dialysis, hemodynamic status, tolerance to treatment time, tolerance to blood and dialysate flow rates, residual renal function, co-morbidities, sufficiency of vascular access, immunologic and hematologic profiles, increased need to remove specific solutes, necessity of minimizing albumin losses, and impact on quality of life if long-term complications such as dialysis-related amyloidosis can be lessened through use of a specific high performance membrane.

The priming volume of a dialyzer may also be a consideration because a low priming volume requirement allows the use of the patient's own blood to prime the circuit without serious hypovolemic effects.⁶² In a typical adult patient this parameter may be of little consequence, but it could be important for children or small adults.¹⁴

There is an increasing demand in dialysis therapy for new measures of biocompatibility such as reducing intradialytic blood pressure variability, decreasing oxidative stress, and delaying the onset or progression of complications. Such selectivity based upon individual patient needs has been referred to as patient-oriented dialysis which also factors in the effects of the membrane upon the patient's quality of life.²⁹ Accordingly, Sanaka, et al, recommend choosing a HPM by balancing the solute removal capacity needed for the patient with the severity of complications, which should be considered a surrogate marker for biocompatibility.⁶³

THE EFFECT OF DIALYZER CHOICE ON COST, HANDLING, STORAGE, AND THE ENVIRONMENT

Single-use dialyzers provide the advantage of reducing the cost of personnel, technician training on dialyzer reuse, reuse record keeping, room maintenance for safety and sterilization, and quality assurance programs. Single use also benefits patients by decreasing reuse syndromes caused by residual germicides. Synthetic membranes with improved biocompatibility have reduced first use syndromes, especially now that sterilization with ETO has been replaced with gamma radiation, electron beam radiation, and steam.^{64,65}

There is also an economic benefit to single-use dialyzers because of the decreased need for space, and the provider can realize savings in utility bills and dialyzer reuse supplies. Legal costs are reduced with increased patient safety, especially with sterilization methods

such as oxygen-free gamma radiation which limits the oxidation of free radicals.⁶⁴

With the development of smaller, more compact dialyzers, the provider can save space and storage costs, while producing less waste and creating less of a burden on the environment.⁶⁴ The manufacture of smaller dialyzers requires the use of less petroleum which is better for the environment, along with the use of plastics from degradable polymers instead of conventional oil-based polymers such as polycarbonate, thus contributing to cleaner waste disposal.⁶⁵ The elimination of toxic materials in dialyzers such as DEHP also leads to safer hemodialysis waste disposal.⁵⁸

Dialyzers that are reused should be reprocessed following the Association for the Advancement of Medical Instrumentation (AAMI) Standards and Recommended Practices for reuse of hemodialyzers.^{2,66} Dialyzers intended for reuse should have a blood compartment volume not less than 80% of the original measured volume or a urea (or ionic) clearance not less than 90% of the original measured clearance.²

*Please note that a new KDOQI Guideline on Hemodialysis Adequacy, which includes the topic of dialyzer membranes, is anticipated for publication in 2014.

DISCLAIMER

Information contained in this National Kidney Foundation educational resource is based upon current data available at the time of publication. Information is intended to help clinicians become aware of new scientific findings and developments. This clinical bulletin is not intended to set out a preferred standard of care and should not be construed as one. Neither should the information be interpreted as prescribing an exclusive course of management.

Variations in practice will inevitably and appropriately occur when clinicians take into account the needs of individual patients, available resources, and limitations unique to an institution or type of practice. Every health care professional making use of information in this clinical bulletin is responsible for interpreting the data as it pertains to clinical decision making in each individual patient.



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