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Membrane Requirements for High-Flux and Convective Therapies

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Abstract

Worldwide, high-flux dialysis (HF-HD) has now surpassed low-flux dialysis (LF-HD) as the predominant treatment modality, recognition that removal of larger uremic retention solutes is desirable for the treatment of patients with end-stage chronic kidney disease (CKD). An even more advanced form of HF-HD in terms of removal of a broad spectrum of uremic toxins is on-line hemodiafiltration (HDF), involving convective transport mechanisms for solute removal. With the modality reaching considerable technical maturity over the last two decades, on-line HDF is now recognized for its clinical efficiency and effectiveness, versatility and safety. Such has been the success of on-line HDF that, in Europe, more patients are treated with on-line HDF than even peritoneal dialysis. Fabrication of high-flux membranes for convective therapies is more than a matter of simply making the membrane 'more open' or of increasing the membrane pore size which is not the only determinant for achieving higher convection. While convective transport of larger uremic retention solutes primarily demands membranes with high hydraulic permeability and sieving capabilities, the making of a modern dialysis membrane involves several other considerations that culminate in the delivery of an effective and safe therapy. In this communication I outline the essential membrane requirements and principles for solute removal by convection, as well of meeting additional features related to the therapy. The basic principles of the membrane manufacturing processes by which desired membrane morphology is derived for the separation phenomena involved in dialysis are further described. An awareness of this enables one to appreciate that, depending on the individual constituents and variations of the manufacturing processes, fabrication of all high-flux membranes entails achieving a balance between the ideal or desired criteria for blood purification. Dialysis membranes for convective therapies, even from the same base polymer, exhibit significant differences in their morphology and thus in their ability to facilitate convection.

The availability, in 1983, of the Fresenius polysulfone membrane was a landmark not only in the history of Fresenius Medical Care but also of dialysis therapy [1]. At a time when the biocompatibility debate caused considerable uncertainty about the long-term application of cellulose-based membranes, the timely introduction of polysulfone as a versatile dialysis membrane material had an additional impact [2]. It facilitated the revival of more efficient, high-volume treatment modalities that had already been shown to realize better blood cleansing but were limited by the unavailability of appropriate technology, including for membranes [3]. Suitable membranes are a prerequisite for modern high-efficiency dialysis therapy modalities to ensure high blood purification and safety.

Membrane Matters in Hemodialysis

Worldwide, high-flux dialysis (HF-HD) has now surpassed low-flux dialysis (LF-HD) as the predominant treatment modality. This, alone, is recognition that more efficient modes of blood purification are beneficial and desirable for the treatment of patients with end-stage chronic kidney disease (CKD) [4]. With prescription of therapies using high-performance membranes expected to increase further, modern membranes need to meet distinct criteria to ensure maximal efficiency and safety in order to enhance patient outcomes over extended periods. The general criteria that define an ideal dialysis membrane have been described previously [5]. With the advent of more advanced treatment modalities in routine dialysis, the needs of modern dialysis membranes have undergone change in recent years. For these therapies, the following three main requirements – all pertaining to membranes – need to be considered (fig. 1a):

The Need to Balance Removal of Larger Toxins with Prevention of Protein Leakage

Efficient removal of excess water and uremic retention solutes ('uremic toxins') that contribute to the uremic syndrome by affecting multiple systems and organs remains the foremost objective of all dialysis therapies. However, ascertaining in vivo toxicity of a given compound is difficult and controversial [6]. Uremic toxins are a heterogeneous group of substances in terms of their source, biological role or significance, association with other proteins and size [7]. Ever since its conception, dialysis is still essentially based on size exclusion principles, that is, the size of uremic toxins in relation to the mean size of the 'pores' of a membrane determines which substances are retained or are able to traverse the membrane barrier. Many factors and conditions influence the size-based transport of substances from the blood to the dialysate compartment, and vice versa [8]. Knowledge of the size range of substances to be removed from uremic blood is

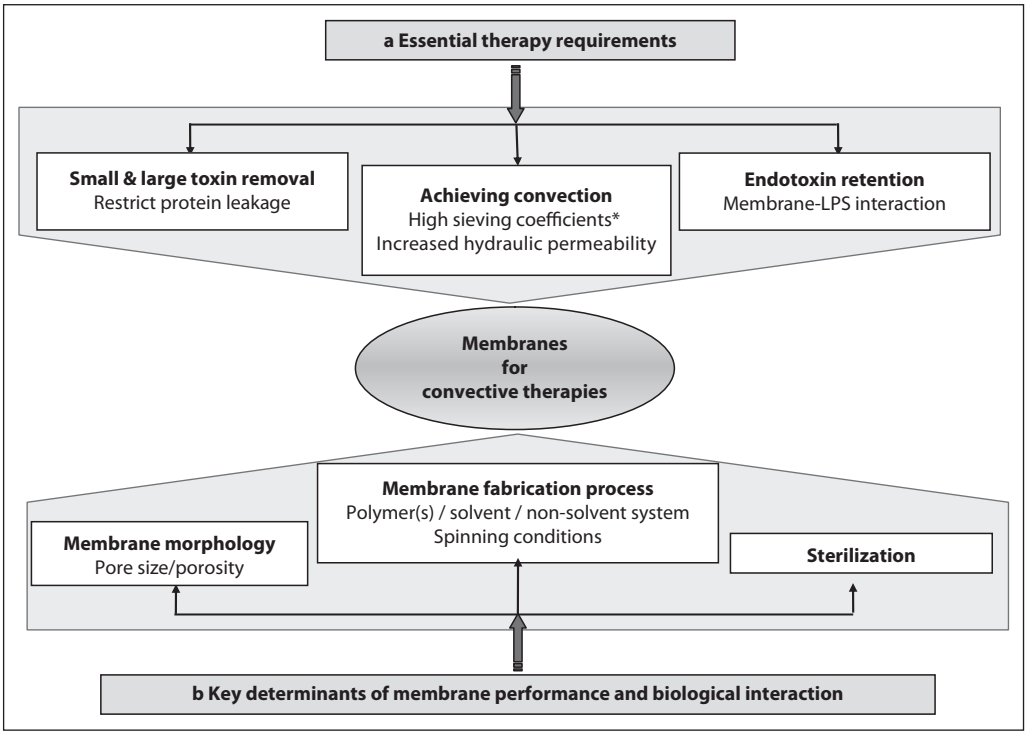

Fig. 1. Essential therapy requirements (**a**) and key determinants of membrane performance and biological interaction (**b**).

thus desirable for the development of appropriate membrane structures. There are other inadvertent mechanisms by which some of the uremic toxin load may additionally be 'removed' during the dialysis. Adsorption of proteins to membrane materials has been well documented and studied, with some membrane materials having a demonstrably higher propensity to overall adsorption of plasma proteins [9]. However, in the opinion and experiences of this author, the phenomenon is highly non-specific, involves virtually all proteins present in blood including those that have little involvement with uremia, varies from one treatment and patient to another and is of minor significance for most dialysis membranes [10]. Furthermore, detecting and quantifying membrane-adsorbed proteins is besieged with methodological difficulties and only monoclonal antibodies are able to identify, or adequately quantify, the constituent proteins of the adsorbed layer.

Considerable advances have been made in recent years in the understanding uremic toxicity. Since its formation in 2000, the European Uremic Toxin (EUTox) Work Group has contributed towards the compilation and classification of an

impressive list of substances that are retained in uremia and deemed to be uremic toxins [7, 11]. Newer analytical techniques such as proteomics have enabled an extension of this compilation [12]. Studies examining the kinetics of removal of specific substances reveal the complexity of solute transport from different compartments and aid selection of treatment conditions to facilitate their removal. However, despite such endeavors to ascribe biological significance to individual substances, the extent to which therapeutic strategies have specifically improved or new potential strategies developed as a direct consequence of these deliberations and knowledge is a point of contention. The fact remains that the uremic syndrome can neither be attributed to nor alleviated by removing selected substances, irrespective of how toxic a given substance may be shown to express. The proliferation of studies showing mere associative rather than causal relationships between individual 'uremic toxins' and morbidity-mortality only serves to distract from the non-specific nature of HD therapies. Of the numerous solutes retained and implicated in uremia, only a few (e.g. water, sodium, phosphate, perhaps β_2-microglobulin) could, with a degree of unanimity, be considered uremic 'toxins'. Increased knowledge on uremic toxicity thus reiterates that uremia is attributed to several substances – *small and large* – some perhaps as yet to be identified. In essence, this was advocated when the 'middle molecule hypothesis' was first proposed [13]. With the knowledge we now have and considering how dialysis functions, it is thus more pertinent to consider strategies that remove – as efficiently as possible – the entire size spectrum of uremic toxins regarded as essential to overcoming the effects of uremia and without incurring high albumin loss – rather than consider looking for and targeting specific substances [14]. Difficult as it presently may be, strategies which enable proteins to shed uremic retention solutes bound to them would appear to be much more effective means of achieving enhanced detoxification and improving dialysis therapies [15].

The Need to Achieve More Convection and Larger Exchange Volumes

Once the necessity to eliminate diverse small and large substances is acknowledged, of the available strategies and factors that effect their removal, foremost is the selection of the appropriate treatment modality. Thereafter, other means such as increasing dialysis time (duration) and frequency of treatment as well as selection of treatment conditions such as blood flow according to the individual needs of individual patients are considered to optimize the effectiveness of each treatment session.

Hemodialysis treatment modalities are commonly classified according to membrane 'flux' (from Latin *fluxus, a flowing*, and variant of *fluere*, *to flow*). The term, together with the prefixes 'low' or 'high' is an indication of the size range of substances a particular membrane or dialyzer is able to remove, i.e. of its relative permeability. As such, low- or high-flux membranes or therapies are highly general terms and do not allude to any specified or defined size ranges

of uremic toxins – which themselves are also arbitrarily and variously classified according to solutes being small, middle or large. Such is the generality of the terms 'low flux' and 'high flux' that it is often overlooked that developments in membrane technology, together with product positioning strategies of industry, has led to a change in the meaning and perception of the terms over recent years. Membranes once considered as high flux only a decade or two ago are now categorized as low flux with the consequence that considerable confusion arises during interpretation of published data. In the HEMO Study, for instance, where the effects of flux and dialysis dose on patient survival were examined, dialyzers allocated to the high-flux group can, according to European perspectives, essentially be adjudged as low flux [5].

Patients requiring hemodialysis have the option of the following treatment modalities: LF-HD, HF-HD, HDF (hemodiafiltration) or HF (hemofiltration). Each modality differs in terms of the extent to which it relies on diffusion and convection, the two predominant solute transport mechanisms in dialysis [17]. Adsorption (affinity of molecules for membrane material), as mentioned, is theoretically the third mechanism of removal occurring more by chance than by specific design and cannot precisely be catered for in any of the four treatment options. Thus, the size range (of solutes) as well as magnitude of their removal varies among the four modalities and the treatment conditions selected for each therapy. Diffusive transport, driven by differences in concentrations in the blood and dialysate compartments, has the limitation that the rate of diffusion in free solution decreases with increasing molecular weight [18]. Thus, the relative contribution of diffusion to overall transport decreases the larger the solute. Diffusion also decreases with increasing membrane wall thickness [18]. Convection, which is the predominant mechanism of solute removal across the glomerular membrane, is a consequence of ultrafiltration of fluid across the dialysis membrane wall having a specified structure [17–19]. Ultrafiltration, in turn, is affected by a number of factors such as transmembrane pressure gradient and properties of blood (flow, hematocrit and blood viscosity, plasma proteins, etc.). Both diffusion and convection are determined by the morphological characteristics of the dialysis membrane, i.e. the dimensions (pore size) and structure (degree of porosity) of the membrane wall [8, 20].

To explain diffusion and convection (solute transport) in relation to membrane structure, it is best to conceptualize the membrane wall (mostly 30–40 μm thick) as a dual-layered barrier across which mass transfer is induced: the thin ('skin'), innermost (blood-contacting) region and the bulk 'support' region [21]. The former is also referred to as the separating or sieving region as the dimensions of the pores therein ascertain the size of the substances in the blood that can traverse the membrane and thereby important towards regulation of convective transport. The structure (thickness, degree of porosity or tortuosity) of the latter is important for both diffusion rates and for ultrafiltration [21]. Thus, unlike low-flux membranes, high-flux membranes permit in addition to

diffusion, considerably higher convection. An estimate of the contribution of convection to solute transport is most commonly achieved by multiplying the solute sieving coefficient by the ultrafiltration rate [18]:

$C_{convective}$ = Sieving coefficient (SC) × Ultrafiltration rate (UFR)

The sieving component is determined by the mean pore size at the innermost separating region of the membrane, defining which molecules are retained or are able to traverse the membrane ('cleared'), that is, by the SC for a given molecule [22]. The SC of a specified molecule for a particular membrane is calculated by the solute concentration of the fluid after being filtered by the membrane divided by the difference in the concentration of the solute in fluid (plasma) entering and exiting the dialyzer ($SC = 2\ C_F/C_{Pi} + C_{Po}$). The actual magnitude of convective transport (excluding any effects of adsorption) then depends on how high the UFR rate is, that is, the hydraulic permeability attributed to the support region of the membrane wall [18]. In summary, convection is the extent to which solutes (depending on their sieving at the separating region of the membrane) are 'dragged' along by the removed fluid (depending on hydraulic permeability of the support region of the membrane).

For the four treatment modalities in question, diffusive solute transport decreases in this order: LF-HD ~ HF-HD ~ HDF ~ HF. Solute transport in LF-HD is predominantly based on diffusive principles, having in reality a minor convective component depending on pore dimensions [18]. Conversely, convective transport decreases in this order: HF ~ HDF ~ HF-HD ~ LF-HD, with HF (without fluid in the dialysis compartment) being purely convective, having the highest [18–20]. High-flux membranes are thus used for all modalities except for LF-HD.

Convection and Blood Cleansing: The Significance of Large Exchange Volumes

In convective therapies like HF and HDF, convective transport is maximized by extensive ultrafiltration beyond the volume needed to achieve dry weight [19]. To benefit fully from the convective component for blood purification, large fluid volumes need to be utilized [23]. By operating at peak UFR relative to the blood flow rates achievable for individual patients, high convective clearances for the larger uremic toxins can be achieved [19]. With the availability of large quantities of highly pure dialysis and substitution fluids, prepared 'on-line', UF volumes well beyond 15 liters are commonly realized. Increased convection and removal of large quantities of fluid have been associated with several clinical advantages pertaining to decreased uremic toxin load, anemia correction, reduction of calcium-phosphate product, improved hemodynamic stability and vascular stability and to lower inflammation, an underlying condition of most diseased states. The degree of convective transport is thus decisive from an overall clinical point of view; by removing (and replacing) larger volumes of fluid from the patient during on-line HDF (the most efficient treatment modality

removing small and large solutes), more efficient blood cleansing is achieved. Consistent with mechanistic considerations, the results of three independent studies involving large numbers of patients have indicated that a survival advantage is evident with high-volume on-line HDF [24–26]. The volume of substitution, a surrogate of the convective dialysis dose, may thus be considered as a critical factor that may impact patient mortality rates.

The Need to Ensure Safety When Exposing Patients to Large Quantities of Fluids
Typically, at a dialysis fluid flow rate of 500 ml/min, the patient is exposed to some 360 liters of dialysis fluid per week (4 h, 3 times per week), compared to approximately 15 liters/week of fluid intake in individuals with normal renal function. Treatment with on-line HDF may require as many as 25 liters of water per treatment, and if both the frequency and duration of the sessions are increased, the total volume of fluid patients are exposed to is therefore considerable. Thus, the entire production of high-purity dialysis and substitution fluids – from the tap to the patient – involves several steps including water purification systems and special ultrafilters as well as dialyzers with high endotoxin-retention capabilities that ensure chemical and microbiological purity of large volumes of fluid contacting the blood of patients.

Bacterial contamination of dialysis fluids gives rise to endotoxins which have been postulated to adversely impact dialysis outcomes through the stimulation of the inflammatory responses and pathways resulting in oxidative stress. Endotoxins, chemically lipopolysaccharides, are derived from the outer wall of Gram-negative bacteria during cell growth and lysis. During dialysis, they could enter the blood compartment of dialyzers via back-transport (mainly back-filtration) mechanisms. Activation of leukocytes results in the generation of pro-inflammatory cytokines and reactive oxygen species, both of which contribute to cardiovascular disease. Recommendations for the maximum permissible levels of microbiological contamination in terms of bacterial colony-forming units (CFU/ml) and endotoxin units (EU/ml) have been proposed for both water and dialysis fluids. The European Best Practice Guidelines for HD recommends the usage of pure water complying with the standards for all forms and treatment types [27].

Microbiological purity and safety of dialysis fluids is achieved by using special ultrafilters (e.g. DIASAFE® Plus) containing hollow-fiber membranes having a high adsorptive capacity for endotoxins. The endotoxins are retained onto materials such as polysulfone predominantly by the mechanism of hydrophobic-hydrophobic interaction, that is, the hydrophobic part of the endotoxins (the fatty acid chain of the lipid A molecule) binds with the hydrophobic domains of the polysulfone polymer [28]. Ultrapure water is obtained by integrating two such ultrafilters in the dialysis fluid pathway of dialysis machines. The filters can be repeatedly disinfected and used for up to about 100 treatments, or up to a period of 12 weeks. An additional and final line of defense is afforded by certain dialyzers

containing hollow-fiber membranes made from synthetic polymers such as polysulfone. A number of studies have shown significant differences between dialysis membranes, even when they are manufactured from the same base polymer, in terms of their safety and ability to prevent passage of endotoxins [22].

The Fabrication of Membranes Meeting the Needs of Modern Convective Therapies

Increasing convection requires membranes having an appropriate structure to enhance removal of larger uremic toxins. Contrary to popular belief and opinion, it is not simply a matter of making the membrane 'more open' or of 'increasing the membrane pore size' which is not the only determinant for achieving higher convection. While convective transport primarily demands high sieving capabilities for larger uremic retention solutes as well as high hydraulic permeability, fabrication of modern membranes involves many other considerations that culminate in the delivery of a safe and effective therapy to the patient (fig. 1b):

Essentials of the Membrane-Making Processes

While one does not need to know how an appliance or a technology is made or functions to be able to use it, an appreciation of the fundamental principles involved nevertheless enables the user to derive maximal benefit from it, or even recognize the limitations. The aforementioned membrane features and functions (e.g. pore size, porosity, sieving ultrafiltration, convection, endotoxin retention, etc.) are frequently and extensively alluded to in the literature, yet rarely in the context of how sophisticated scientific principles and manufacturing conditions transform raw materials into medical devices that replace the functions of a healthy organ.

Fabrication of Membranes by Phase Inversion [29] – The Polymer/Solvent/Non-Solvent Triad

Hollow-fiber membranes are fabricated by the so-called spinning technology similar to the spinning of fibers for textiles. The process involves the controlled transformation of a polymer from a liquid to a solid state. Following selection of the appropriate polymer (or a blend of polymers) for a particular application, the first step is to dissolve the polymer(s) in an appropriate solvent to form a polymer solution. The process of solidification occurs by the transition from one liquid state into two liquids, and at a certain stage during de-mixing the high polymer concentration phase will solidify to form a solid matrix. This is done by injecting the polymer solution through the inner tube of a high-precision spinneret (which determines fiber dimensions) and the emerging fiber is immersed in a coagulation bath containing non-solvent. Here, precipitation occurs as a result of the exchange of solvent with non-solvent which essentially 'extracts'

the solvent from the solution leaving behind a 'scaffolding' structure. By carefully controlling the initial stages of the phase separation processes, the desired membrane morphology for both the innermost separating region (sieving function) and of the support region (ultrafiltration) is derived – according to the desired degree of convection and (target) size range of the uremic toxins that need to be removed.

The Choice of the Polymer System for Convective Membrane Fabrication

The choice of the polymer has, historically, significant implications and connotations regarding the properties it ascribes to the membrane as well as to its impact on the quality or outcome of the therapy. Selection of an appropriate polymer for dialysis membrane manufacture goes beyond the search for alternative polymers instigated by the bioincompatibility of early dialysis membranes made from cellulose, now defunct. The demise of cellulose-based dialysis membranes in the 1980s was further accelerated by the recognition that, unlike cellulose, synthetic materials such as polysulfone were much more versatile in enabling membrane fabrication for convective therapies and removal of middle molecules – both of which were essentially revived because of advancements in technology and a desire to achieve enhanced detoxification [5, 22]. The selection of the polymer begins with its suitability for the phase separation processes that rely on a series of complex thermodynamic principles involving the chemical and physical properties of the spinning solution. Factors such as solution composition, miscibility, homogeneity, viscosity, temperature, humidity, residence time during precipitation, etc., all need to be considered for the selected base polymer. Further, in dialysis where blood compatibility-related issues provoked the search for alternative materials, polymer blends have to be used to attain the hydrophilic-hydrophilic balance for optimal blood-material interactions. Polyvinylpyrrolidone is the most common co-polymer of most modern synthetic dialysis membranes to construe this balance although its usage impacts membrane structure as well [29]. Although chemical and thermal resistance to sterilizing agents (e.g. steam, ethylene oxide and irradiation) are considered at the outset of the polymer(s) selection process, endotoxin-retention capabilities of dialysis membranes are only discernible with the finished product (the dialyzer). Should this crucial prerequisite not be met satisfactorily, the entire membrane-spinning process has to be re-evaluated in terms of revised polymer composition, membrane-spinning conditions, membrane morphology and performance, biocompatibility and endotoxin-retention testing.

Conclusion

Convective therapies are successfully used to treat patients with CKD and acute renal failure [30]. Hemodiafiltration is a treatment modality applied to 14% of

Fig. 2. Leading with verve and skill: Emanuele Gatti has instigated and motivated ideas and innovation to promote OL-HDF by his hands-on approach. Membrane and fibre technology remains a priority under his watchful eye (here demonstrating the art of making wicks from beeswax).

all CKD patients on regular renal replacement therapy in Europe in 2010 and, as such, significantly more patients received HDF than peritoneal dialysis in Europe. Following its conception and early validation, much of the success in the clinical implementation of on-line HDF is to be attributed to technological enterprise, including creating membranes fulfilling functions other than simple sieving demanded by this treatment modality. The contribution and vision of individuals, from scientists and physicians to those in industry, who have steadfastly believed in the virtues of hemodiafiltration for the benefit of the patient, cannot be ignored, and is to be applauded (fig. 2).

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