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Flummoxed by flux: the indeterminate principles of haemodialysis

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ABSTRACT

In haemodialysis (HD), unwanted substances (uraemic retention solutes or 'uraemic toxins') that accumulate in uraemia are removed from blood by transport across the semipermeable membrane. Like all membrane separation processes, the transport requires driving forces to facilitate the transfer of molecules across the membrane. The magnitude of the transport is quantified by the phenomenon of 'flux', a finite parameter defined as the volume of fluid (or permeate) transferred per unit area of membrane surface per unit time. In HD, as transmembrane pressure is applied to facilitate fluid flow or flux across the membrane to enhance solute removal, flux is defined by the ultrafiltration coefficient (KUF; mL/h/mmHg) reflecting the hydraulic permeability of the membrane. However, in HD, the designation of flux has come to be used in a much broader sense and the term is commonly used interchangeably and erroneously with other measures of membrane separation processes, resulting in considerable confusion. Increased flux is perceived to reflect more 'porous' membranes having 'larger' pores, even though other membrane and therapy attributes determine the magnitude of flux achieved during HD. Adjectival designations of flux (low-, mid-, high-, super-, ultra-) have found indiscriminate usage in the scientific literature to qualify a parameter that influences clinical decision making and prescription of therapy modalities (low-flux or high-flux HD). Over the years the concept and definition of flux has undergone arbitrary and periodic adjustment and redefinition by authors in publications, regulatory bodies (US Food and Drug Administration) and professional association guidelines (European Renal Association, Kidney Disease Outcomes Quality Initiative), with little consensus. Industry has stretched the boundaries of flux to derive marketing advantages, justify increased reimbursement or contrive new classes of therapy modalities when in fact flux is just one of several specifications that determine membrane or dialyser performance. Membranes considered as high-flux previously are today at the lower end of the flux spectrum. Further, additional parameters unrelated to the rate of diffusive or convective transport (flux) are used in conjunction with or in place of KUF to allude to flux: clearance (mL/min, e.g. of β_2-microglobulin) or sieving coefficients (dimensionless). Considering that clinical trials in nephrology, designed to make therapy recommendations and guide policy with economic repercussions, are based on the parameter flux they merit clarification—by regulatory authorities and scientists alike—to avoid further misappropriation.

Keywords: flux, haemodialysis, hydraulic permeability, membranes, pore size, ultrafiltration

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INTRODUCTION

In haemodialysis (HD), elimination of unwanted substances (solutes or 'uraemic toxins') retained in uraemia is achieved by their transport across a permselective barrier (the membrane) from the blood to the dialysis fluid compartment [1]. All separation processes, whether occurring in the body between cells and tissue or in extracorporeal circuits, involve various driving forces that facilitate the transfer of molecules across membranes [2–4]. The magnitude of the transport from one compartment to the other is determined by the phenomenon of 'flux' and it essentially refers to the 'permeability' of the membrane [5]. Flux, or permeation rate, in all industrial or medical membrane-based separation processes is a finite parameter to quantify transport phenomena and is defined as the volume (amount) of fluid (or permeate) transferred per unit area of membrane surface per unit time (e.g. L/m^2/h) [6]. In addition to the driving force(s) present, created or applied externally, flux is also influenced by the physiochemical characteristics of the semi permeable membrane relative to those of the solutes to be removed. As in the body, the primary driving force in HD is diffusion, created by the net movement of substances from a region of higher concentration (blood) to a region of lower concentration (dialysis fluid). Further, when transmembrane pressure (TMP) is applied to increase the flow of fluid across the membrane to enhance solute removal, flux is then represented as mL/h/mmHg, the ultrafiltration coefficient (KUF) and a measure of the water or hydraulic permeability of the membrane [6, 7].

Although flux is a finite phenomenological and mathematical entity that is elementary to all membrane separation processes as a measure of the rate of transport, in HD the designation has come to be used in a much broader and loose sense and further qualified by prefixes such as low-, mid-, high-, super- or ultra-flux without scientific scrutiny or reasoning. The term flux is used interchangeably with other measures of HD separation processes or features (e.g. clearances, sieving characteristics) of membranes. The sieving coefficient (SC; for a selected molecule), a ratio without dimensions, is often used to specify or categorize flux of membranes either on its own or in conjunction with the KUF. This lack of distinction between a measure of fluid transport properties of membranes and an index that reflects the ability of molecules to traverse the membrane based on their size (i.e. sieving) has created an ambiguity that even confounds interpretation of data from clinical trials. Most commonly, and erroneously, flux is perceived simply as a reflection of pore size only; membranes with increased flux are equated to 'larger' pores for the enhanced removal of larger uraemic toxins during HD [8–12]. Two membranes having similar 'water flux' (hydraulic permeability) can have different clearances of solutes such as β_2-microglobulin (β_2-m) due to differences in pore size.

We describe the principles and interrelationship between transport mechanisms and membrane features that determine both the selectivity and rate of removal of uraemic toxins of various sizes during HD. Today, the distinction between low- or high-flux dialysis modalities is not easily apparent and increasingly difficult to discern because of variable and changing designations and shifting boundaries of flux. The designation of flux has significant ramifications in terms of not only influencing the prescription of therapy, perceived efficiency and benefits of treatment and effect on patient outcomes, but also has economic repercussions in determining reimbursement rates. The confusion and implications around the term flux are thus not trivial and require resolution.

MEMBRANE TRANSPORT PROCESSES APPLIED TO THE REMOVAL OF URAEMIC RETENTION SOLUTES

In every membrane separation process, the membrane acts as a permselective barrier or interface between two phases or compartments; separation is achieved when one component is transported more readily than other components across the membrane. Transport between compartments and across the membrane occurs because a force acts on individual components or molecules [6]. The extent of this driving force (X) is determined by the gradient or difference in potential (ΔX) across the membrane divided by the membrane (wall) thickness (ℓ):

$$\text{Driving force} = \Delta X / \ell.$$

In membrane separation applications, the potential difference (ΔX) arises from differences in pressure (ΔP), temperature (ΔT), electrical energy (ΔE) or, in the case of dialysis, concentration gradients (ΔC) [6, 13].

The landmark middle molecule hypothesis, so embedded in diverse facets of uraemic toxicity and HD, was in essence a consequence of this fundamental 'law' of membrane separation processes [6, 14, 15]. Membranes available to researchers at the time the hypothesis was proposed were several times thicker than those in use today, thereby restricting removal of larger unknown uraemic retention solutes (URS), designated the 'middle molecules' (MM), an ill-defined expression that still prevails [15, 16]. From the equation above, the driving force achieved for transport of molecules across early dialysis membranes was thus low and only small water-soluble compounds could be dialysed [15].

However, greater wall thickness was not the only factor responsible for the poor removal of larger solutes, as other membrane characteristics and dialysis conditions further determine the extent to which a given membrane allows selective passage of substances across its wall [17]. In HD, other than the driving force prevalent (concentration gradient) or imparted (TMP), complete membrane morphology determines the overall performance or efficiency of the therapy [18, 19]. The two key determinants of transport across membranes are selectivity (i.e. what can or cannot go through the membrane) and the flow (i.e. how much fluid goes through and at what rate is a solute removed from blood) [5–7, 17, 20]. It is the latter, denoted flux or permeation rate, that provides the main driving force and is often the source of some confusion, as there are different ways of describing and expressing, and hence interpreting, this parameter. Without resorting to overly complex equations that are used to quantify transport phenomena and often hamper comprehension, the distinguishing features of the two parameters need to be recognized [5, 6]. Selectivity of separation in HD, like in most filtration applications, is fundamentally based on the size of the components (URS, some of which express toxicity) to be separated; several physical attributes of the membrane discriminate between two types of molecules (i.e. transported more readily) because of the relative differences in size [17, 19]. Once the transmembrane passage of solutes is possible, the efficiency (or performance) of the entire therapy system will be determined by the bulk motion of the fluid—flux—the magnitude of which is influenced by several conditions applied during the therapy and membrane properties.

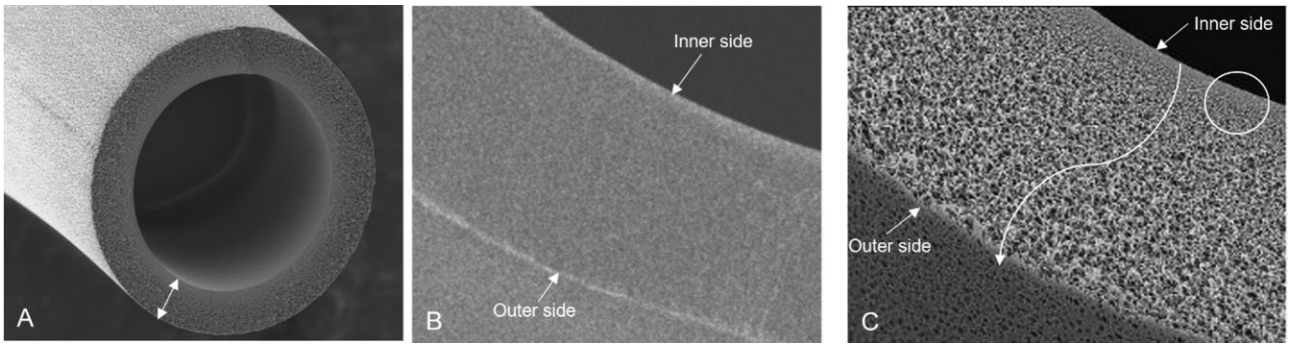

FIGURE 1: (**A**) (Double arrow) The hollow fibre membrane wall across which solute transport occurs. (**B**) A symmetric membrane wall structure with a high wall thickness and low overall porosity (both of which are not conducive to passage of larger uremic retention solutes)—the type of membrane on which the middle molecule hypothesis was based [14]. (**C**) Wall structure of a modern asymmetric membrane with increasing porosity (wavy arrow) from the inner blood-contacting wall to the outer dialysis fluid side.

MEMBRANE SEPARATION DETERMINANTS BASED ON FLUX

The membrane transport phenomena perspective: determinants of flux

Membrane flux (originating from the Latin fluxus, meaning flowing, and fluere, meaning to flow), or permeation rate, is defined as the volume of permeate produced per unit area of membrane surface per unit time (L/m^2/h or mL/m^2/h) [6]. The relationship between flux and the driving force is given by:

$$\text{Flux} = \text{Diffusion Coefficient} \times \text{Driving Force}(\Delta C)$$

Such a relationship is expressed by Fick's law, which relates mass flux to a concentration difference with the diffusion coefficient, a proportionality constant, being a measure of how fast (efficiently) an individual component diffuse across the membrane [6]. Such phenomenological equations are generally like black boxes that reveal little about the physical or chemical nature of the membrane or how the transport is related to the membrane structure. In HD, flux is thus directly proportional to the concentration gradient, which is the difference between the concentration of a solute in the blood and dialysate compartments and is maintained by having fresh dialysis fluid flow that ensures solute concentrations are lower on the dialysis fluid side compared with the blood compartment.

Flux is indirectly proportional to the viscosity and total or overall resistance (R_T) attributed to three resistances of mass transfer: blood compartment (R_B), the membrane (R_M) and the dialysate compartment (R_D) [21, 22]:

$$R_T = R_B + R_M + R_D.$$

together with viscosity, is inversely proportional to flux [6]:

$$\text{Flux (permeation rate)} = \frac{\text{Driving force}}{\text{Viscosity}\,(\eta) \times \text{Total Resistance}\,(T_R)}$$

Of the three resistances that contribute to a decrease in flux, membrane resistance (R_M) has the greatest impact and the morphology-related features that contribute to R_M are shown in Figure 1. First, as mentioned above, the greater the wall thickness of the membrane, the greater the distance a molecule must traverse (Figure 1A). The second factor that also contributed to the poor clearance of larger substances leading up to the proposal of the middle molecule hypothesis was the membrane structure, i.e. the porosity (amount of polymer relative to the open spaces) and type of channels (oval, finger-like or vacuoles) in the membrane wall from the lumen to the outside. Membranes available and used at the time of the hypothesis (like cuprophan) had a symmetric membrane structure, i.e. the membrane structure from the inner to the outer side was uniform, with the result that the high resistance to mass transfer was determined by the total thickness of the membrane (Figure 1B). The wall thickness of membranes available at the time was considerably larger compared with those in use today (~25–40 μm), increasing diffusive resistance especially for larger molecules. In comparison, almost all membranes in use for HD today are asymmetric, consisting of a very dense innermost (separating) layer surrounded by a gradual increase of porous regions towards the outer membrane wall that facilitate transport of solutes to the dialysis fluid compartment (Figure 1C) [23]. The pore density in the innermost separating layer thus determines the primary resistance (and transport rate) while the remainder, the porous sublayer acting as the support scaffolding, also offers resistance to fluid and solute transport, i.e. decreasing resistance and increasing ease of transport of both [19]. The final factor influencing the resistance is the degree of tortuosity of the transport channels as fluid and solutes make their journey from the inner blood to the outer dialysate compartment (Figure 1C).

Of the two non-membrane structure-related types of resistance (R_B and R_D) that result in a decline of overall flux, R_B represents the greater contribution to the reduction of flux. Within milliseconds of the interaction of blood with artificial surfaces, several plasma proteins (especially albumin, fibrinogen, immunoglobulin G, etc.) are adsorbed to the membrane surface [24–26]. The intensity of the interaction and the composition of the protein layer are determined by the surface chemistry and charge of the membrane material(s) at this interface [27]. Resistance to mass transfer resulting in a decline of flux is the result of two related phenomena [6, 28, 29]. In the phenomenon of concentration polarization, a certain retentivity of solute occurs because plasma fluid passes through more readily, resulting in higher local solute concentrations in the vicinity of the membrane surface than in bulk flow [6, 23]. In unconducive conditions, especially involving perturbations of blood flow or TMP, the adsorbed protein layer that lies between the membrane and the concentration polarization layer may lead to plugging of pores, increasing resistance further and severely diminishing flux [21, 28, 29].

So far we have examined only the concentration gradient as the driving force, but in HD another force is involved to enhance the transport of larger solutes from the blood to dialysis fluid

compartment. Ultrafiltration is a pressure-driven mechanism to increase flux (fluid transport) across the membrane and instead of hydraulic permeability (flux units of L/m^2/h) the volumetric filtration rate per mmHg is expressed in the form of the KUF (in mL/h/mmHg) [6, 7, 17, 30]. It is a value derived from *in vitro* measurements whereby bovine or human blood is ultrafiltered at different transmembrane pressures [31]. For the so-called high-flux membranes, at lower TMPs (~0–100 mmHg), a linear relationship exists between the ultrafiltration rates (UFRs), but plateaus at relatively high TMPs (>150 mmHg); the KUF is derived from the linear part of the plot. It should be noted that the KUF is not normalized with respect to surface area and it is a property of the dialyser, not just the membrane; a dialyser with membranes containing relatively small pores can have a high KUF if the surface area is large [7, 30].

Flux (*J*; hydraulic permeability), as expressed by the Hagen–Poiseuille relationship, is directly proportional to this second driving force (i.e. the applied TMP), the fourth power of the mean pore radius (r^4), and inversely proportional to length of the fibre (l) and viscosity (η). Thus the largest impact is from pore size and small changes in pore size lead to significant effects on hydraulic permeability [6, 17]:

$$\text{Flux } (J) = \left(\frac{\pi \times r^4}{8 \times \eta} \frac{\Delta_P}{l}\right)$$

It is important to note that while the Hagen–Poiseuille equation is a good general description of transport (flux) across the membrane wall consisting of parallel pores, in reality very few membranes possess such ideal geometric structures [6]. Most depictions of 'pores' are idealized; in reality their pathway towards the outside of the membrane wall follows tortuous zigzag channels [19, 32]. Likewise, the theoretical estimation of flux provided by such equations is compromised in real life as there is a significant decrease in flux over time; flux decline (discussed below in detail) is usually so severe that it is a fraction of that measured for water (hydraulic) permeability, which is measured in the laboratory under standardized conditions [31].

To summarize, the concept of flux, fundamental to the functioning and designation of various HD therapy modalities that derive their names from this term, is a highly complex and multifactorial transport phenomenon. The hydraulic permeability—flux—of a membrane varies with the membrane thickness, pore size distribution and pore density [7]. Thus it is not the easiest of concepts to comprehend, or to describe or control in real life. Consequently flux is perceived, expressed and portrayed variably, with little consensus within various sectors of the dialysis field.

Distinguishing low from high flux: the regulatory body/guidelines perspective

US Food and Drug Administration (FDA). The 1998 Centre for Devices and Radiological Health (CDRH, a branch of the FDA) guidance for premarket notifications for conventional and high-permeability haemodialysers was one of the early formal attempts to define the boundaries of flux for dialysers [33, 34]. The FDA specified that the *in vitro* KUF for a conventional haemodialyser would be ≤12 mL/h/mmHg. A 'conventional haemodialyser' (FDA regulation 21 CFR 876.5820) was described as one having a semipermeable membrane with sufficiently low permeability to water so that an ultrafiltration controller will not be required to prevent excessive loss of water from the patient's blood. The *in vitro* KUF for a 'high-permeability haemodialyser' would be >12 mL/h/mmHg, as described in the 2018 updated FDA regulation (21 CFR 876.5860): 'this highly permeable membrane may also permit greater loss of higher molecular weight substances' [35]. The dialysate delivery system for these high-permeability haemodialysers requires the use of an ultrafiltration controller to regulate the rate of removal of water from the patient's blood. It must be noted that today in routine dialysis, such a step is not carried out, as all machines are equipped with automatic volume-controlled ultrafiltration that regulates the amount of fluid removed or KUF according to patient needs. Despite this, the current FDA designation (CFR 876.5860, dated April 2020) states that the high-permeability system consists of a semipermeable membrane with an *in vitro* KUF >8 mL/h/mmHg, that is, even lower than the previous guidelines [36].

European Renal Association (ERA). The European Best Practice Guidelines (EBPG) on Dialysis Strategies was published in 2007 under the auspices of the ERA, providing guidance on four facets of dialysis delivery, including one entitled Flux and convection (Guideline 2.1) [37]. The use of high-flux HD (low-flux HD) was recommended 'to delay long-term complications (dialysis-related amyloidosis, poor phosphate and anaemia control and increased cardiovascular risk) of haemodialysis'. Further, haemodiafiltration (HDF) or online HDF (OL-HDF) were recommended to 'exploit the high permeability of high-flux membranes'. While expressing caution at the level of evidence in the studies used for setting the guideline, the beneficial clinical consequences of increasing flux to enhance removal of middle molecule compounds were clearly outlined, including the survival benefits for convective therapies. However, the entire guideline is devoid of any mention of the criteria to define or distinguish between low- and high-flux membranes. The omission is more perplexing given that the authors delve into some detail of the findings of the American HEMO Study that distinguished low from high flux as KUF being below or above 14 mL/h/mmHg, respectively, i.e. above either the current value of 8 or the previous 12 mL/h/mmHg set by the FDA [38, 39]. Unsurprisingly, no major benefit from the use of high-flux membranes was observed in the HEMO Study.

Subsequently in 2010, ERBP Advisory Board, the official guideline body of the ERA, recommended the use of high-flux membranes based on the findings of another, more soundly planned large-scale randomized controlled trial, the European Membrane Permeability Outcomes (MPO) Study, examining flux as the major outcome parameter [40, 41]. The guidance of the revised Guideline 2.1 was thus to use high-flux membranes for 'all patients, high-risk (serum albumin <40 g/L) as well as low-risk ones, even though the evidence to support the use of high flux in patients with low risk was lacking'. Inexplicably for a guideline, again no details are given as to what exactly constitutes low- or high-flux membranes. Hence two major trials addressing flux as their core investigative parameter (HEMO and MPO studies) portrayed distinctly different definitions of high-flux [42].

Guideline 5 (haemodialysis membranes) of the KDOQI Clinical Practice Guideline for Haemodialysis Adequacy: Update 2015. In the KDOQI guideline, use of high-flux membranes is recommended based on three large randomized controlled trials testing the hypotheses that high-versus low-flux dialysers could improve survival or cardiovascular outcomes in patients undergoing maintenance HD [43]. The KDOQI recommendation was based on the findings, in addition to those of the HEMO and

Table 1. Different definitions and perceptions of low- and high-flux membranes in clinical trials examining the effects of membrane flux on patient outcomes (morbidity and mortality)

Clinical study (Reference) (year)	Low-flux KUF definition (mL/h/mmHg)	High-flux KUF definition (mL/h/mmHg)	Guideline in which study was incorporated
HEMO [39] (2002)	≤14	≥14	EBPG[a]/KDOQI[b]
MPO [41] (2009)	≤10	≥20	EBPG[a]/KDOQI[b]
EGE [44] (2013)	16/18	46/59	KDOQI[b]

Details of the studies are provided in the text.

[a]Tattersall J, Martin-Malo A, Pedrini L *et al*. EBPG guideline on dialysis strategies. *Nephrol Dial Transplant* 2007; 22: ii5–21 (supported by position statement in Reference [40]).

[b]National Kidney Foundation. KDOQI clinical practice guideline for haemodialysis adequacy: 2015 update. *Am J Kidney Dis*. 2015;66(5):884–930 [43].

MPO studies, of a third trial comparing low- versus high-flux dialysers, the EGE trial [44]. Again, in the EGE study there was no statistically significant difference in the primary outcome between high-flux (KUFs of 46 and 59 mL/h/mmHg) and low-flux dialysers (KUF of 16 and 18 mL/h/mmHg) (Table 1). Thus, despite three large RCTs designed specifically to address the issue of flux (showing no significant differences in survival between patients on low- or high-flux membranes in terms of the primary outcomes), guidelines recommend high-flux without defining it.

Position of some other guidelines on flux. The UK Renal Association Clinical Practice Guideline on Haemodialysis recommends that patients with minimal residual function should be treated with high-flux dialysers, but specification of the boundaries of flux are not specified [45]. Similarly, the Kidney Health Australia-CARI guidelines recommend the use of high-flux dialysers without providing specifications to distinguish between low and high flux [46]. Thus, for practitioners seeking evidence on which to base their judgement of whether to apply high flux in clinical practice or seeking guidance on the boundaries that separate low- from high-flux therapies, confusion prevails.

Distinguishing low from high flux: the scientific literature perspective

The overriding target of dialysis therapies is to improve the short- and long-term well-being of patients by removing fluid and diverse unwanted substances retained in uraemia ('uraemic toxins') as efficiently as possible. Among the various strategies (e.g. increasing time and duration of treatment sessions, choice of treatment modality) to improve detoxification of uraemic blood, treatment-related factors (blood and dialysis fluid flow rates) as well as the choice of the membrane/dialyser have received the most attention in HD [37, 47, 48]. The demarcation between the concept of high-efficiency dialysis (using 'high-permeability membranes') and low- or high-flux dialysis is still arbitrary and has changed over time. The concept of highly permeable membranes gained impetus during the 1970s following landmark investigations showing that diffusive removal of smaller substances could be supplemented by convective techniques (haemofiltration) to remove the 'middle molecules' (a term in vogue at the time) [49, 50]). Soon thereafter, coupled with the blood-incompatibility tag of the conventional cellulosic membranes of the era, synthetic polymer-based membranes with increased permeabilities brought about a paradigm shift in dialysis with the development of the polysulfone membrane in the mid-1980s [51, 52].

In 1995 Akizawa *et al*. [53] proposed a membrane classification scheme based on 'performance' parameters of diffusion, ultrafiltration and SC (discussed in detail in the section Distinguishing low from high flux: the industry perspective). High-flux membranes (defined as KUF ≥10 mL/min/mmHg) were distinguished vaguely from high-permeability membranes as having, in addition, a 'high SC' for unspecified 'low molecular weight protein fractions'. In an alternative classification, Golper *et al*. [54] define conventional dialysers (i.e. low flux) as having a KUF <15 mL/min/mmHg and high flux as having a KUF >15 mL/min/mmHg. Table 2 lists some other definitions of high versus low flux based on KUFs from the literature, underlining the divergence in the perception as to what high (or low) flux is. Both the HEMO and MPO studies generated an immense volume of literature and from both studies *post hoc* secondary analysis led to some clinical distinction in terms of benefits of increased flux and to changes in guidelines as mentioned above. Thus, even though both trials were inconclusive in terms of distinguishing outcomes based on flux, their contentious and different flux 'boundaries' are regularly cited in the literature [39–42].

Distinguishing low from high flux: the industry perspective

Manufacturers of membranes and dialysers have an incentive to offer products exhibiting superior features to justify higher prices. The competitive resolve has, over the decades, resulted in dialysers that are safer, more biocompatible, environmentally friendly and incorporate innovative design refinements to optimize blood and dialysis fluid flows under different demanding therapy conditions. Features underpinning the collective performance (i.e. clearance, KUF, sieving properties and surface areas) of a dialyser are the centrepiece of all product manufacturer specification sheets of dialysers. It is this designation and categorization of the product that primarily influences the decision making of the user as the devices are, again, arbitrarily linked to therapy modalities.

Flux 'sells', and the greater the impressions created of it being higher, the greater the perception of a device's superior performance in terms of its detoxification capabilities and hence the effectiveness of the therapy itself. Product labelling often entails a company-specific tradename together with number-letter combinations signifying differences (e.g. surface area) within a dialyser range on the technical data sheets. However, it is conventional for each manufacturer to position a given product range according to a flux-therapy category, e.g. low-, mid- or high-flux dialysis, or for HDF. This is a highly arbitrary exercise and done mostly based on the KUF (sometimes with sieving properties discussed below) and regarded to equate to the overall performance to assess flux or transport even though KUF only represents the hydraulic permeability of the

Table 2. A selection of the KUF-based classification of the flux of dialysers in different studies reported in the literature, indicating a lack of consensus within the community and the arbitrary nature of classification of 'flux'

	Flux (mL/h/mmHg) specification			
First author (Reference) (year)	Low[a]	Mid	High	Comments
Akizawa *et al.* [53] 1995	>3		>5	
Clark and Ronco [17] 2001	<12	12–30	>30	
Ronco and Clark [21] 2018	8		>30	Presumably, membranes between 8 and 30 are mid-flux
HEMO Study [39] 2002	<14		>14	
Ward [75] 2005	<6		20–40	Designation for KUF 6–20 not specified
MPO Study [41] 2009	<10		>20	In the study, groups were clearly separated: low-flux = 9.8 mL/h/mm Hg; high-flux = 44.7 mL/h/mmHg[b]
Tatterasall and Ward EUDIAL [47] 2013			>20	
Golper [54] 2017	<15		>15	
Haroon and Davenport [76] 2018	<10	10–20	>20	

[a]Low flux sometimes described as 'conventional' or 'standard' dialysers relative to high flux.
[b]Unlike the HEMO Study, the difference between the KUF values for the low-flux versus high-flux patient groups was statistically significant.

devices, as explained. Table 3 shows the KUF (flux) values of a selection of commercial dialysers from some of the larger manufacturers (the list is intended as an example only; no attempt has been made to list all suppliers or dialysers).

Table 3 reveals that the KUF values of the high-flux dialysers, ranging from 20 to 102 mL/min/mmHg, and between 8 and 22 mL/min/mmHg for low-flux dialysers. Thus, considering the FDA definition of high flux >8/12 mL/min/mmHg, all dialysers in commercial use are high flux. If one takes the ERBP/KDOQI limit of 20 mL/min/mmHg as defining high flux, one sees that certain dialysers categorized as low flux are in the high-flux category. Table 3 data may appear misleading, as KUF values specified by manufacturers are dependent on the surface area of each device. The larger the surface area, the higher the KUF, as larger dialysers have more membrane (fibres) within the filter housing to cover prescription needs of patients of a wide body size and blood flow range.

The issue of having to make some sort of correction for the KUF values according to dialyser surface area is moot for two reasons. First, bearing in mind the KUF values for the flux categories specified in some guidelines, there is the inclination to place a dialyser in either the low or high category if the manufacturer-specified value is below or above the specified value; expert groups or bodies that establish such guidelines do not correct for the surface area dependency of KUF. Second, the perception is that the greater the surface area, the higher the KUF, the higher the flux and the better the removal of uraemic toxins for the patient. Table 3 shows higher KUF values for some smaller dialysers compared with larger surface areas from other suppliers. Boundaries of flux are thus inconsistent and keep changing; dialysers deemed high flux in the past based on KUF are today at the lower end of the low-flux spectrum.

Adjectival flux: low-, mid-, high-, super- ultra-flux designation of dialysers

The renaming of the original 'square-meter-hour hypothesis' [aptly describing that the product of membrane surface area (m^2) and the time (h) spent on treatment was theoretically predictive of clearance of larger uremic toxins] to the 'middle molecule hypothesis' is revealing of the dialysis community's penchant towards reducing (profound) scientific concepts or entities to more general terms that are imprecise in their connotation [15]. To this day, it is not patently clear which molecules merit the 'middle' molecule designation and vague terminology like 'smaller' or 'larger' middle molecules abound in the literature, leading to confusion and misappropriation [16]. Likewise, it is now commonplace to use, adjectives like 'low-', 'mid-', 'high-' and 'super-' to qualify flux (a finite parameter descriptive of transport phenomena in membrane separation processes) rather arbitrarily. Table 3 reveals the randomness of the categorization of devices into classes low-, mid-, high- and super-flux by manufacturers for product differentiation (defined in economic terms as the marketing of generally similar products with minor variations that are used by consumers when making a choice). Although the 'industry' may have been instrumental in the creation of the vague boundaries describing flux, the scientific community has been quick to embrace such designations and terms such as super-flux or even super-high-flux have been propagated without discernible examination or objection [55–63]. For example, if one takes the super-flux designation of one manufacturer as having a KUF of 48 mL/min/mmHg (Table 3), then a significant proportion of commercial dialysers mentioned in the table may be categorized as 'super-flux'.

Redundancy of KUF as a practical tool for present-day dialysis therapies

As the need for and acceptance of dialysers with higher permeability increased in the 1980s, defining the hydraulic permeability (i.e. KUF) became relevant from a practical view point. In clinical practice, the TMP (mmHg) had to be monitored during each dialysis session to achieve the required UFR to remove a prescribed amount of fluid accumulated during the interdialytic interval (based approximately on the weight gain). However, unlike low-permeability dialysers where the UFR/TMP plots are linear, higher-permeability dialysers express a curvilinear relationship and a separate curve each having different blood flow rates. The TMP required each time was read off charts (provided by dialyser manufacturers) plotting ultrafiltration rate (mL/min) versus TMP (mmHg). An appreciation of the factors involved around the KUF/hydraulic permeability concept was necessary if not mandatory for physicians and nurses [34, 64]. Today, this knowledge is irrelevant, as all machines are equipped with

Table 3. KUF designations and dialyser types

Company/designation KUF (mL/h/mmHg)	Dialyser type (surface area, m^2)							
Asahi	APS-13U (1.3)	APS-15U (1.5)	APS-18U (1.8)	APS-21U (2.1)				
KUF	53	59	67	75				
Asahi/Rexeed	Rexeed 13A (1.3)	Rexeed 15A (1.5)	Rexeed 18A (1.8)	Rexeed 21A (2.1)	Rexeed 15A (2.5)			
KUF	66	72	81	90	102			
Baxter high-flux HDF	Revaclear 300 (1.4)	Revaclear 400 (1.8)	Revaclear 500 (2.1)					
KUF	48	54	65					
Gambro/HDF high-flux	Polyflux 140H (1.4)	Polyflux 170H (1.7)	Polyflux 210H (2.1)					
KUF	60	70	85					
Gambro/low-flux	Polyflux 14 L (1.4)	Polyflux 14 L (1.7)	Polyflux 14 L (2.1)					
KUF	10	12.5	15					
B Braun/high-flux	Pro 13H (1.3)	Pro 16H (1.6)	Pro 19H (1.9)					
KUF	70	85	97					
B Braun/low-flux	Pro 13L	Pro16L	Pro 19L					
KUF	11	14	17					
FMC/high-flux	FX40 (0.6)	FX50 (1.0)	FX60 (1.4)	FX80 (1.8)	FX100 (2.2)			
KUF	20	33	46	59	73			
FMC/low-flux		FX5 (1.0)	FX8 (1.4)	FX10 (1.8)				
KUF		8	12	14				
FX–HDF			FX600 (1.5)	FX800 (1.8)	FX1000 (2.2)			
KUF			52	63	75			
Fresenius/high-flux	FX Cordiax 40 (0.6)	FX Cordiax 50 (1.0)	FX Cordiax 60 (1.4)	FX Cordiax 80 (1.8)	FX Cordiax 100 (2.2)	FX Cordiax 120 (2.5)		
KUF	21	33	47	64	74	87		
Fresenius/HDF			FX Cordiax 600 (1.4)	FX Cordiax 800 (1.8)	FX Cordiax 1000 (2.2)			
KUF			46	62	76			
Nikkiso/high-flux	FDX-120GW (1.2)	FDX-150GW (1.5)	FDX-180GW (1.8)	FDY-210GW (2.1)				
KUF	47	52	57	64				
Nikkiso/super-high-flux	FDY-120GW (1.2)	FDY-150GW (1.5)	FDY-180GW (1.8)	FDX-210GW (2.1)				
KUF	48	54	59	64				
Nipro/high-flux	Elisio 09H (0.9)	Elisio 11H (1.1)	Elisio 13H (1.3)	Elisio15H (1.5)	Elisio 17H (1.7)	Elisio 19H (1.9)	Elisio 21H (2.1)	Elisio 25H (2.5)
KUF	53	59	64	67	74	76	82	93
Nipro/medium-flux		Elisio 11M	Elisio 13M	Elisio 15M	Elisio 17M	Elisio 19M	Elisio 21M	
KUF		15	17	20	22	25	27	
Nipro/low-flux		Elisio 11M	Elisio 13M	Elisio 15M	Elisio 17M	Elisio 19M	Elisio 21M	
KUF		11	14	16	18	20	22	
Nipro-Superflux3				Sureflux 15FH SF (1.5)				
KUF				66.9				
Nipro Superflux				Sureflux 150L LF (1.5)				
KUF				12.8				

Industry sets its own standards for the classification of flux for reasons of product differentiation. Arbitrary ranges are established as well as the use of adjectives such as ‘super’ to classify flux. Low flux of one manufacturer may be high flux for another and vice versa. Each company determines its own range of KUF for its dialyser product portfolio according to their business strategy.

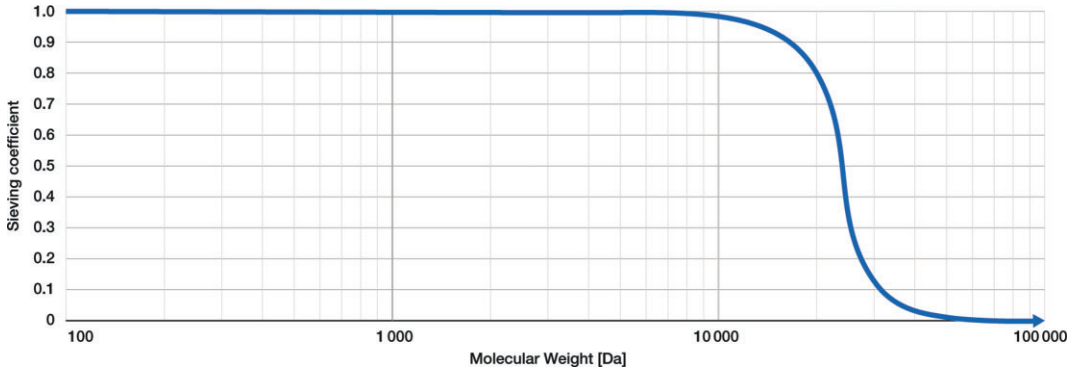

FIGURE 2: The sieving profile of a typical 'high-flux' dialysis membrane indicating the extent to which molecules (based on their molecular weight) are able, or unable, to traverse the membrane wall. An SC of 1 means it can pass unimpeded across the membrane (in this case, molecules just <10 000 Da), while an SC of 0 implies it is too large (relative to mean pore size) to pass across the membrane wall (in this case, ~40 000 Da). Between these two extremes (the sigmoidal part of the curve), the extent to which molecules are removed depends on their size (Da); the smaller the molecule, the easier its ability to traverse the membrane wall.

automated volume-controlled ultrafiltration mechanisms to achieve a steady ultrafiltration rate throughout the session [34]. Only the duration of the therapy session and the target weight loss need to be entered into the machine at the outset, and while the KUF value is displayed on the machine at any point, it is rarely looked at. Hence the main parameter governing transport processes in HD and a cornerstone concept of flux is more of a scientific concept (for therapy classification) and of commercial value rather than having practical or clinical relevance [34].

MEMBRANE SEPARATION DETERMINANTS BASED ON SELECTIVITY

Flux, the hydraulic permeability of the membrane that is quantified by the KUF, facilitates the transport—and rate—of water and substances across the width of the membrane. Which substances are, or are not, able to pass the membrane ('sieving' function) depends predominantly on the size, geometry and distribution of the pores at the innermost separating region of the membrane relative to the size (and conformation) of the molecules to be removed or retained. Like flux, which can be expressed mathematically in different ways, membrane selectivity, another measure of the 'performance' of a membrane, is expressed by two different but closely related concepts of solute retention or rejection [6, 21].

Membrane retention—the sieving function

Human kidneys produce >4 million litres of virtually protein-free primary urine in a lifetime and in healthy individuals the sieving process is accomplished by the glomerular filter without the smallest sign of clogging, even in old age [65]. Understanding the sieving process is a prerequisite to understanding the pathogenesis of proteinuria (the leakage of plasma proteins into the urine), which is the hallmark of glomerular disease and a major risk factor for systematic cardiovascular complications [65, 66]. In renal physiology, the sieving process accomplished by the glomerular filtration apparatus is expressed as the clearance per unit ultrafiltration rate, usually for albumin, as a marker of proteinuria. This is calculated from the glomerular SC (GSC) for albumin:

$$GSC_{Albumin} = C_B/C_P,$$

where C_B is the concentration in Bowman's capsule and C_P is the concentration in systemic plasma. A low GSC indicates that the glomerular filtration barrier severely restricts the filtration of albumin.

Just as an understanding of the sieving processes in the glomerulus by fenestrated capillaries is a prerequisite to understanding the pathogenesis of proteinuria, an understanding of the sieving function of dialysis membranes is equally informative, as an 'opening up' of the membrane structure (larger pore sizes) results in uncontrolled and high loss of albumin, an undesirable characteristic of dialysis therapies using highly porous membranes [67]. Dialysis membranes need to possess extremely low SCs for albumin to restrict leakage into the dialysis fluid [68].

The sieving characteristics of membranes are described by the sieving coefficient (SC) profile, which is a measure of how easily substances of different sizes are able to pass from the blood to the dialysate compartment [6, 21]. It is the ratio of the concentration of a given solute in the filtrate (C_f) and its concentration in plasma water (C_p):

$$SC = C_f/C_p.$$

The sieving properties of membrane range from 100% (or SC = 1), i.e. solute passes freely through the membrane (or 0% retention of solute in blood), to 0% (SC = 0), meaning solute cannot pass through membrane at all (100% retention of solute in blood) (Figure 2). The primary consideration here is the size of the molecule in relation to the mean size of the pores of a particular membrane at the innermost, blood-contacting region of the membrane. The pores of any membrane, at the separating region, have a size distribution with a certain proportion of pore sizes below or above the mean value [17]. The size—and geometry—of the pores of each membrane depend on the production process of the manufacturer. The main determinants are the choice of the polymer systems and the thermodynamic membrane 'spinning' conditions [6, 7, 69, 70].

It should be noted that the SC profile of a given membrane is derived from laboratory measurements using polydisperse dextrans of different molecular weights as surrogates of solutes that need to be removed during HD [71]. Thereafter, knowing the molecular weight of the molecule of interest, its SC is read off the vertical axis to provide an estimation of its predicted removal *in vivo*. Several factors contribute to the non-correlation between the *in vitro* estimations and the *in vivo* reality. The main factors are the phenomena of concentration

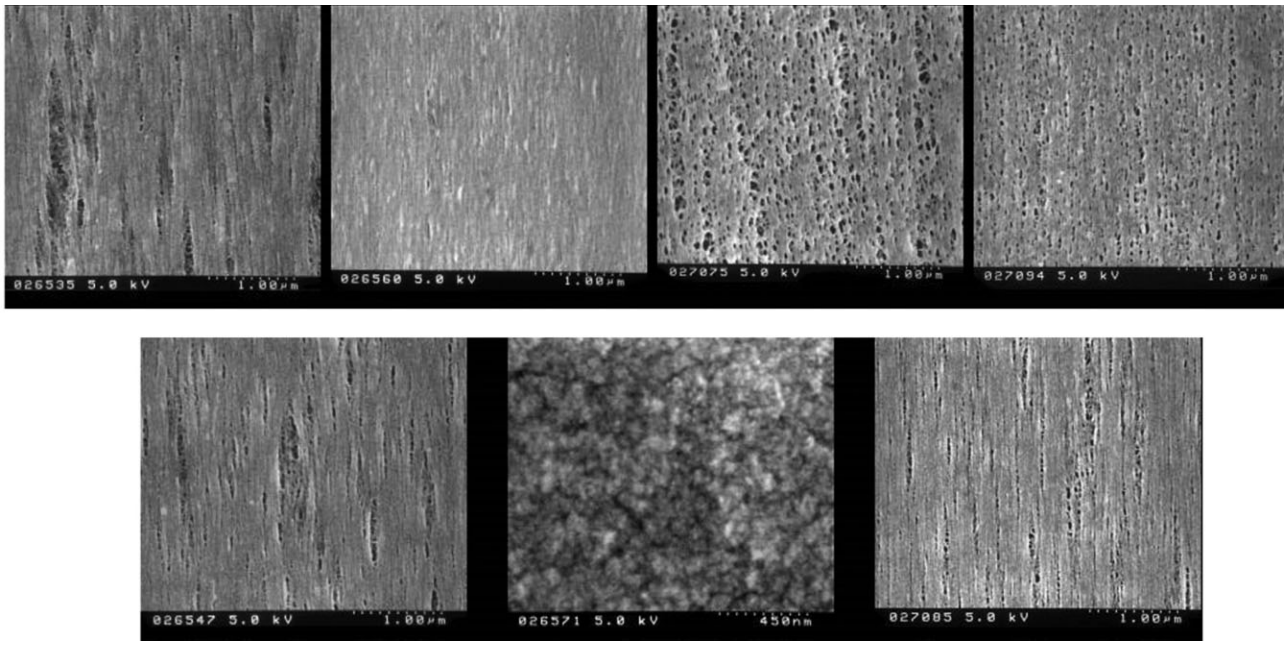

FIGURE 3: Scanning electron micrographs of inner (blood contacting) surfaces of seven high-flux HD membranes from different manufacturers. The scales indicate 1 μm (in 100-nm units), except for one membrane in the lower panel (middle micrograph) for which the scale is 450 nm (in 45-nm units). Highly variable inner region structures are apparent for the different high-flux membranes commonly used in clinical practice, ranging from discernible pores of various sizes to long gaps and fissures several times the size of the albumin molecule. Remarkably, all manufacturers claim essentially comparable properties with respect to the removal of larger uraemic toxins and minimal loss of albumin.

polarization, membrane surface chemistry and the adsorption of plasma proteins on the blood-contacting membrane surface effectively causing a narrowing or sometimes complete plugging of the pores [28]. This decrease in the sieving characteristics of a membrane in the clinical setting is also affected by the operating conditions (e.g. blood flow rate TMP) and patient characteristics (e.g. blood viscosity). SC values are thus merely *in vitro* estimations of the predicted passage or removal of solutes (e.g. creatinine, vitamin B_{12}, β_2-m and albumin) across the membrane wall in the clinical situation.

Figure 3 shows the diversity of surface morphology of the inner blood-contacting surfaces, revealing structures ranging from clear open pores of various sizes distributed uniformly to diffuse gaps without discernible pore-like structures or having large fissure-like 'tears' on the surface. Remarkably, manufacturers of all these commercial membranes make essentially similar claims regarding the specificity or selectivity of solute removal, 'uniformity' of pore size and geometry, 'narrow pore size distribution' and the absence of excessively large pores may that result in leakage of larger useful proteins, particularly albumin during HD [72]. Using the scale indicating 100-nm units (except for one membrane, lower panel, middle micrograph in Figure 3), it is possible to estimate the pore sizes or degree of porosity of each membrane type. If the size (Stokes radius) of albumin is taken as 3.5 nm/35 Å (and disregarding the protein coating that forms and changes constantly throughout the duration of the treatment or the effects of TMP), a substantial number of pores several times the size of the albumin molecule would result in its leakage. Thus it is not simply a matter of increasing membrane pore size as is commonly alluded to when discussing uraemic toxins to enhance removal of larger substances, especially middle molecules [5, 12, 63, 73, 74]. While larger mean pore size does lead to easier passage of larger molecules, mere enlargement of pore dimensions is simplistic and a poor reflection of the quality of dialysis membranes and their capabilities. As the scanning electron microscopy pictures in Figure 3 also show, membrane pores do not conform to the generally envisaged geometry, i.e. one of oval perforations of uniform size distributed evenly on the inner membrane surface [19]; the membrane morphology–solute removal relationship is far more complicated. Thus, while analogous to the glomerular sieving processes, the SC profile of a given membrane is only a useful estimation aid indicating the extent to which a range of molecules could be eliminated, or retained, according to their size rather than providing precise information of the passage of a molecule with a defined molecular weight.

Classification of membranes according to flux, i.e. hydraulic permeability (KUF) that as described above is highly contentious, as its boundaries are being constantly redefined, gets even more distorted when the SC concept is used to define low- versus high-flux dialysis. Although classification of membranes based on performance measures that included SCs goes back to the mid-1990s, it was the HEMO and MPO trials that led to the extrapolation of the definition of the flux of membranes to include β_2-m clearance and SCs to create a multi parameter categorization of the flux of membranes [39–42, 53, 54, 75]. In their guidance towards choosing a dialyser, Haroon and Davenport [76] even appear to suggest that β_2-m clearances alone can be used to distinguish dialysers of different flux: 'low-flux, mid-flux and high-flux dialysers were defined as having β_2-m clearances of $<$10, 10–20 and $>$20 mL/min, respectively', or 'also sometimes defined a β_2-m SC of $>$0.6'. In the Japanese healthcare system, the β_2-m clearance capabilities of dialysis membranes are used for dialyser reimbursement purposes, although the categorization is not linked to the flux concept [79] (Table 4). Five categories have been established and the higher

Table 4. Classification and membrane designations used for the Japanese reimbursement system linked to the clearance of β_2-m and not KUF (mL/min/mmHg)

Reimbursement class	β_2-m Clearance (mL/min)[a]	Reimbursement level	Membrane designation
1	<10	Low	Low-flux
2	≥10–<30	↓	Classic high-flux
3	≥30–<50	↓	High-flux
4	≥50–<70	↓	
5	≥70	High	Super-high-flux

Note the distinction created between the 'classic' high-flux, high-flux and super-high-flux categories. No membrane designation specified for reimbursement of class 4. Each arrow indicates an increase in reimbursement level relative to the previous reimbursement class. Figure modified from Yamashita [79].
[a]Experimental conditions: $Q_B = 200$ mL/min, $Q_D = 500$ mL/min, $Q_F = 10$ mL/min/m^2.

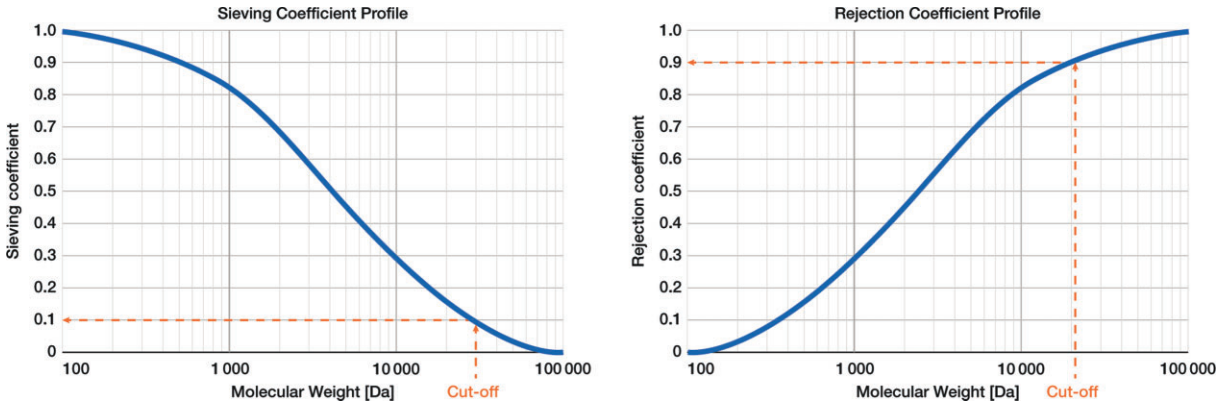

FIGURE 4: Reciprocity of SC and RC profiles of the same membrane to explain the concept of 'cut-off' (see text).

the clearance values for β_2-m, the higher the reimbursement rate [77–79]. While such a reliance on a single uraemic toxin whose kinetics of removal are not representative of other URSs could be disputed and divides opinion, the association of (β_2-m) clearance (mL/min) with flux (mL/min/mmHg) or increased permeability to create yet more subclasses of flux is particularly confounding and sets an undesirable precedent [79].

Membrane rejection—the notion of membrane cut-off

Like the SC principle, the concept of membrane cut-off is sometimes applied as an alternative to indicate the specificity of a membrane as to what can or cannot pass across the membrane. In fact, it is derived from either the SC profile shown in Figure 4 or, more appropriately, from the 'rejection' characteristics of a membrane. The SC is inversely related to the rejection coefficient (RC), as SC is the reciprocal of the rejection coefficient [6]:

$$RC = 1 - SC.$$

Whether membrane selectivity is characterized by its SC or RC profiles, the decisive determinant for both representations is the size distribution of the pores, and both are influenced by protein adsorption, concentration polarization and driving force [23, 25, 80].

The cut-off of a membrane arbitrarily corresponds to an SC of 0.1 (i.e. solute is only 10% filtrable) on the *x*-axis of the SC profile. Reciprocally, using the RC profile of a membrane, cut-off is defined as that molecular weight that is 90% rejected (retained) by the membrane. Unfortunately, cut-off values are often erroneously interpreted in an absolute fashion (e.g. 'this membrane has a cut-off of 30 000') to imply a molecular weight threshold at which molecules greater than that value are retained while those less than are removed. Such a categorical interpretation is both erroneous and misleading. As indicated above, the pores in membranes have a broad size span and are not of one uniform size; thus substances both above and below this single hypothetical value are able to pass the membrane, especially the smaller-sized solutes.

In fact, what the cut-off value really implies is that solutes >30 000 Da are >90% rejected (non-filtrable). In other words, 10% removal of larger solutes >30 000 Da does indeed occur and, for a solute like albumin that is present in large quantities in blood, an appreciable leakage during dialysis could nevertheless occur. This can readily be explained by the fact that the pores in the separating region of the membrane are not of uniform size but have a certain percentage of pores of sizes above (and below) the mean pore size value [17, 19, 81]. Contrary to claims by membrane manufactures, it is evident from Figure 3 that the pore size distribution is not 'narrow' for all membrane types, and the pore size distribution profiles vary considerably according to the method of manufacture. The drawbacks of using the cut-off concept are thus apparent and caution needs to be exercised when using this parameter, especially when interpreted in an absolute way.

CONCLUSIONS

Flux refers to the hydraulic (water) permeability properties of a membrane [6, 21, 30, 31, 34, 54]. Quantified by the KUF, flux has come to be incorrectly used as a measure indicating the ability of a dialyser to remove medium or high molecular weight substances considered as uraemic toxins. The KUF is proportional to applied pressure, and its value depends on

various other membrane features and conditions. So deep-seated is the term flux in decision making in HD that treatment modalities (prescription and reimbursement) as well as clinical trials derive their traits from its usage: low-, mid-, high- or super-flux dialysis therapies reflect ascending effectiveness and superiority of each modality, supposedly leading to increased well-being and better outcomes for the patient.

The use of adjectives as prefixes to a define or qualify a finite and measurable scientific transport phenomenon has, in fact, quite the opposite effect. It relegates the pursuit of scientific exactitude to abstractions, encouraging generalities that compound rather than clarify issues [82]. Flux, in HD, has come to be affiliated with clearance (mL/min), as SC (a ratio, no units) for a single protein or even loss of albumin (g per treatment session) together with KUF (units of mL/min/mmHg) are normally used to quantify transport phenomena across a semipermeable membrane [76]. Depending on the inclination of the authors, for each of these measures, different boundaries are set under various adjectival classes for flux, further blurring an already ill-defined area of dialysis. We have shown that even for KUF, which more aptly reflects flux, there is little unanimity in terms of its boundaries and classifications in the scientific literature, guidelines or industry. Few can discern between high-flux, classic high-flux or super-high-flux dialysis modalities: as indices of the quality of therapy, such imprecision is disconcerting. Over the years, the goalposts for flux keep changing; dialysers previously classified in terms of KUF as high flux are today towards, or even at, the lower end of the low-flux scale.

Regulatory bodies and developers of official guidelines, usually so fastidious in their deliberations, have thus far abstained from laying down the nomenclature and categories for flux in scientific terms to set precise limits of KUF, a finite and measurable parameter describing a defined separation phenomenon. The implications of flux being an imprecise entity go far beyond the realm of semantics; issues pertaining to patient outcomes are at stake, as clinical trials have been and will be designed based on therapy categories using the parameter of flux. Patients' prescriptions too are based on the perception of flux, with higher flux associated with a better detoxification effect. As illustrated in Table 3, low flux could be anything with KUF values up to 20, while high flux could have KUF values >100 mL/min/mmHg. Virtually all dialysers in clinical use today would be high flux if the FDA limit (8 or 12 mL/min/mmHg) or the EBRP limit (20 mL/min/mmHg) is used. Finally, flux categories affect reimbursement criteria in different countries, although in Japan it is based on β_2-m clearances rather than the KUF-based designation of flux. A strong argument against approaches that classify membranes on selectivity criteria (SC-based categorization of flux) is that, unlike KUF, which is a single value for a dialyser, an SC-based categorization of flux of a membrane (or dialyser) could literally have dozens of SC values depending on the molecule in question; theoretically each molecule in blood could be given an SC depending on its size and extent to which it may or may not traverse the membrane. While the SC of β_2-m is the most frequently and is regarded a surrogate for the class of middle molecules, its mass transfer kinetics are not representative of other solutes [83]. Further, a number of methodological variables and limitations influence the SC profiles of membranes, making exact designation of the SC value of a solute difficult [84].

The term and concept of flux, used interchangeably with other measures of membrane 'permeability', performance and efficiency has multiple designations, classifications and boundaries, and hence interpretations. Being a parameter that influences the prescription of therapy modalities (designs of clinical studies depend on its definition), it is an indicator of the effectiveness of treatment that affects outcomes and clinical decision making. As this in turn has economic repercussions by influencing management and reimbursement policies, flux in HD deserves better clarification, by regulatory authorities and scientists alike, to prevent its misappropriation.

SYNOPSIS

1. Categorisation or definition of membranes according to their 'flux' has significant repercussions in terms of HD therapy prescription, design of clinical trials and reimbursement rates.
2. Although flux is a finite parameter reflecting the hydraulic permeability of a membrane (KUF; mL/h/mmHg), dialysis membranes are erroneously classified into flux classes using SC (dimensionless ratio) or clearances (mL/min).
3. The lack of distinction between flux, sieving or clearance to define membranes has led to the creation of arbitrary categories of flux (punctuated with adjectives such as high, low, super, ultra); membranes previously considered high flux based on their KUF are today at the low end of the flux spectrum.
4. In view of the fact that membrane flux impacts dialysis therapy choices, guidelines and economics, there is a major need to establish the precise context for the use of an elementary parameter of HD.

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CONFLICT OF INTEREST STATEMENT

SKB received consultancy fees towards the writing of this article. He is a former employee of Fresenius Medical Care, Germany. FK is an employee of Fresenius Medical Care, Germany.

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