Blood Purification

Hemodialysis – Guidelines

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Standardization of Nomenclature for the Mechanisms and Materials Utilized for Extracorporeal Blood Purification

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Abstract
In order to develop a standardized nomenclature for the mechanisms and materials utilized during extracorporeal blood purification, a consensus expert conference was convened in November 2022. Standardized nomenclature serves as a common language for reporting research findings, new device development, and education. It is also critically important to support patient safety, allow comparisons between techniques, materials, and devices, and be essential for defining and naming innovative technologies and classifying devices for regulatory approval. The multidisciplinary conference developed detailed descriptions of the performance characteristics of devices (membranes, filters, and sorbents), solute and fluid transport mechanisms, flow parameters, and methods of treatment evaluation. In

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addition, nomenclature for adsorptive blood purification techniques was proposed. This report summarizes these activities and highlights the need for standardization of nomenclature in the future to harmonize research, education, and innovation in extracorporeal blood purification therapies.

Introduction

Standardized nomenclature exists to ensure harmony and minimize both ambiguity and miscommunication. When individuals use terms in an uncoordinated manner outside of clear definitions, patient safety issues may arise along with difficulties in therapy comparisons and scientific communication. Clearly, there are instances in which use of non-standardized nomenclature may lead to miscommunication. For instance, some clinicians use the term "ultrafiltration" to describe net removal of fluid from a hemodialysis (HD) treatment, while others use this term to describe the total volume of fluid removed over a given time period. At best, the current situation results in inefficient communication; at worst, it creates potential harm from misunderstanding treatment parameters and inappropriate therapeutic choices. Names and definitions matter. As the complexity of critical care increases, more precise use of nomenclature that eliminates this type of ambiguity is necessary. In 2019, the World Health Organization called for greater standardization of medical device nomenclature with a clear goal of "an international classification, coding, and nomenclature for medical devices that would be available to all Member States and that would support: patient safety, access to medical devices for universal health coverage, quality of health care, and achievement of Sustainable Development Goal 3 (ensuring healthy lives and promoting well-being for all at all ages) [1]." With these goals in mind, a consensus expert conference was convened to provide a detailed description of the performance characteristics of devices (membranes, filters, and sorbents), solute and fluid transport mechanisms, adsorption mechanisms, flow parameters, and methods of treatment evaluation, with a focus on extracorporeal therapies for blood purification.

Methods

The Consensus Conference on Definition, Classification, and Nomenclature Standardization for Extracorporeal Blood Purification Techniques was held over 3 days in Rome, Italy, in November 2022 and included an interdisciplinary group of researchers and clinicians from the following disciplines: adult and pediatric nephrology, adult and pediatric critical care, anesthesiology, and biomedical and chemical engineering. Participants represented Europe, Asia, Australia, North America, and South America. The consensus meeting followed a modified Delphi process as previously utilized for the Acute Disease Quality Initiative consensus meetings [2]. Prior to the conference, participants screened the literature and previous taxonomy efforts [3–8]. Key search words included (but were not limited to) "renal replacement therapy," "kidney replacement therapy," "dialysis," "hemofiltration," "convection," "diffusion," "ultrafiltration," "adsorption," "dose," "blood purification," "renal support," "dialysis membrane," together with the relative Medical Subject Heading (MeSH) terms. Abstracts of articles were screened, and papers were read in full and analyzed. Based on this literature search, a series of definitions and terms were proposed, and consensus was achieved from the majority of experts who participated in the conference. This manuscript details the output of the group regarding key nomenclature and standardization of definitions relevant to the materials and methods utilized in extracorporeal therapies (Table 1, 2).

Mechanisms of Solute and Fluid Removal

Diffusion

Diffusion is the net movement of a solute from a region of higher concentration to a region of lower concentration (Table 3). In dialytic therapies, diffusion can be described as solute transport across a semipermeable membrane produced by a concentration gradient [9]. Diffusion rate is governed by Fick's Law (Fig. 1) [10] and is therefore inversely proportional to the solute's size. In addition, the rate of diffusion is inversely proportional to the length through which the solute crosses (from the bulk of blood to the inner surface of the membrane, through the membrane, and from the outer wall into the bulk flow of dialysate) and to solvent (plasma or dialysate) viscosity. The diffusion coefficient (D) is determined by the Stokes-Einstein equation (Fig. 1) [11].

Ultrafiltration

Ultrafiltration is the transport of the solvent (plasma water) across a semipermeable membrane and is dictated by both membrane characteristics and the transmembrane pressure (TMP) (Fig. 2). The TMP is the pressure gradient across the membrane defined by the hydrostatic pressure in the blood compartment (P_B), the hydrostatic pressure in the dialysate/ultrafiltrate compartment (P_D), and the blood oncotic pressure (π_B). Machine-estimated TMP is an integrated value along the length of the filter and does not reflect the true local pressure profile in the filter. In other words, a positive displayed TMP does not imply a positive TMP at each point in the filter [12].

Table 1. Common dialysis prescription parameters and their definition

Variable	Symbol	Unit	Definition
Blood flow	Q_B	mL/min	Volume of blood per unit of time in the axial (longitudinal) direction through the filter
Plasma flow	Q_P	mL/min	Volume of plasma per unit of time in the axial (longitudinal) direction through the filter, $Q_P = Q_B \cdot (1 - \text{hematocrit})$
Total ultrafiltration	UF^{TOT}	mL	Volume of fluid removed from the patient during a dialysis session
Net ultrafiltration	UF^{NET}	mL	Volume of fluid removed from the patient subtracted by volume of fluid infused to patient during a dialysis session
Total ultrafiltration flow	Q_{UF}^{TOT}	mL/h	Volume of fluid removed from the patient per unit of time
Net ultrafiltration flow	Q_{UF}^{NET}	mL/h	Volume of fluid removed from the patient subtracted by volume of fluid infused to patient per unit of time
Dialysate flow	Q_D	mL/min	Volume of sterile fluid per unit of time delivered into the space between the hollow fibers and the filter housing, i.e., into the dialysate compartment
Pre-filter replacement or substitution flow	Q_R^{PRE}	mL/min (IHD) mL/h (CRRT)	Volume of sterile fluid per unit of time delivered upstream the filter
Post-filter replacement or substitution flow	Q_R^{POST}	mL/min (IHD) mL/h (CRRT)	Volume of sterile fluid per unit of time delivered downstream the filter
Effluent flow	Q_{EFF}	mL/h (CRRT)	In the context of CRRT, $Q_{EFF} = Q_D + Q_R^{PRE} + Q_R^{POST} + Q_{UF}^{NET}$
Filtration fraction	FF	Dimensionless (given in %)	Is the ratio between the volume of fluid per unit of time removed from the patient's blood during its passage through the filter divided by $Q_P + Q_R^{PRE}$ $FF = [Q_{UF}^{NET} + Q_R^{PRE} + Q_R^{POST}] \div [Q_P + Q_R^{PRE}]$

CRRT, continuous renal replacement therapy; IHD, intermittent hemodialysis.

Table 2. Dialysis glossary: suggested terms to describe

Preferred term	Suggested abbreviation	Terms to avoid
Therapies		
Renal replacement therapy	RRT	Kidney replacement therapy (KRT)
Continuous renal replacement therapy	CRRT	Continuous kidney replacement therapy (CKRT), acute dialysis
Intermittent hemodialysis	IHD	Chronic dialysis, acute dialysis (the terms acute and chronic refer to duration of kidney disease rather than duration of dialysis treatment)
Prolonged intermittent hemodialysis or prolonged intermittent renal replacement therapy	Prolonged IHD or PIRRT	Sustained low-efficiency dialysis (SLED), acute dialysis
Hemodiafiltration	HDF	Online hemodiafiltration (OL-HDF) or high-volume online hemodiafiltration
Expanded hemodialysis	HDx	Middle cutoff (MCO) hemodialysis, MCO-HD, protein-leaking hemodialysis, super high-flux hemodialysis, or high-permeability hemodialysis
Isolated ultrafiltration	Isolated UF	Slow continuous ultrafiltration (SCUF)
Disposables		
Filter	–	Membrane, dialyzer, or hemodialyser
Plasmafilter	–	Membrane or plasma filter
Cartridge	–	Filter, resin, sorbent, or column

Table 3. Differences between diffusion and convection, adapted with permission from Pstras, Ronco, and Tattersall (reference 14)

Variable	Clearance by diffusion	Clearance by convection
Size of the molecule and membrane pores	Inversely proportional to the solute hydrodynamic radius and proportional to the effective area of exchange	Proportional to the sieving coefficient (SC), which depends nonlinearly on the ration of solute and pore radii; quasi-independent for solutes with SC close to 1
Thickness of the membrane	Inversely proportional	Independent
Surface area of the membrane	Proportional	Independent
Ultrafiltration flow (Q_{UF})	Nonlinearly inversely dependent (through changes is plasma viscosity)	Proportional
Dialysate flow (Q_D)	Nonlinearly dependent	Independent
Blood flow (Q_B)	Nonlinearly dependent	Independent
Hematocrit	Nonlinearly inversely dependent	Independent
Width of blood and dialysate channels	Inversely proportional to the average distance solute is required to diffuse	Independent

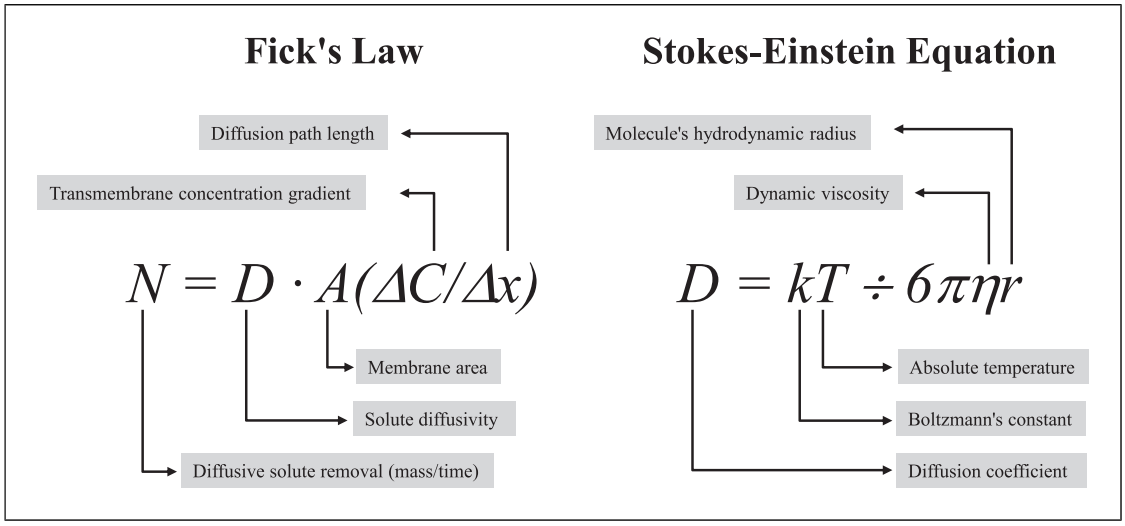

Fig. 1. Diffusive clearance determinants.

Convection

Convection, also termed solvent drag, is the transport of solutes due to the flow of plasma water across a semipermeable membrane (Table 3). Convective transport is dictated by the rate of fluid flow across the membrane (Q_{UF}, ultrafiltration flow) and the ease with which a given solute can permeate the membrane's pore structure, the latter being a function of membrane sieving properties and solute molecular weight. For a given filter membrane and flow conditions, this permeation tends to be inversely proportional to solute molecular weight. Ideally, instead of molecular weight, the calculated molecular radius (Stokes-Einstein radius) [13] or the radius of the sphere circumscribing the molecule better correlates with convective clearance. Nonetheless, for the sake of simplicity, molecular weight is generally utilized [14–17]. Compared to diffusive transport, convective transport permits the removal of higher molecular weight solutes at a higher rate.

Despite being intrinsically related, ultrafiltration (Fig. 3a) and convection are not synonymous (Fig. 3b). The process of ultrafiltration refers to the flux of fluid

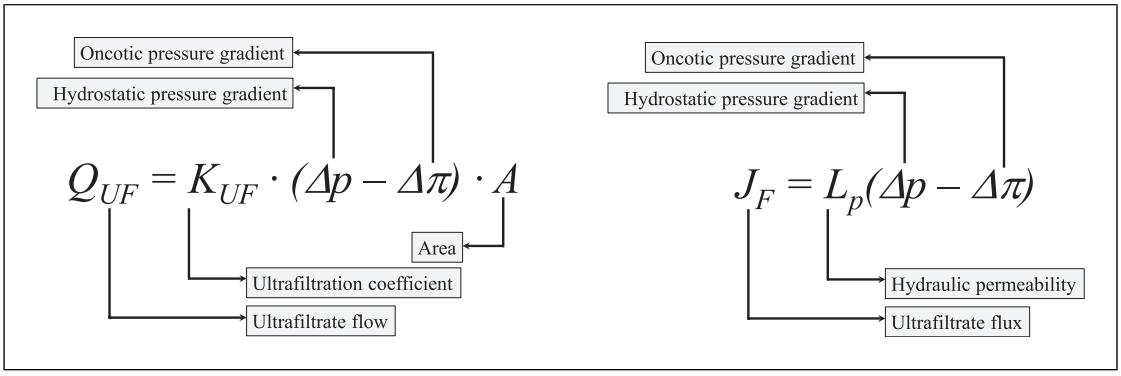

Fig. 2. Ultrafiltration mechanism.

(solvent). Thus, ultrafiltration may generate convective clearance for a given solute, depending on the size of the solute and the size of the membrane pores [9].

Total Ultrafiltration versus Net Ultrafiltration

In clinical practice, the term ultrafiltration is often used by clinicians to describe the net ultrafiltration (volume of fluid removed from the patient) during a dialysis session (Table 1). HD operates by clearing blood of relatively small solutes primarily through diffusion, although some clearance of larger molecular weight solutes occurs by convection clearance, typically through the mechanism of backfiltration (see below). In HD, only the circuit priming volume and saline flushes are infused into the blood compartment. If the intent of a therapy is not to change the patient's fluid balance, total ultrafiltration flow (UF^{TOT}) is the sum of net ultrafiltration flow (UF^{NET}) plus the volume of fluid infused into the blood compartment (circuit priming). For example, if UF^{NET} is desired to be zero and the circuit priming is 0.6 L, UF^{TOT} should be 0.6 L.

In hemofiltration (HF) (pure convective modality) or hemodiafiltration (HDF) (convective and diffusive modality), UF^{NET} equals the volume of UF^{TOT} subtracted by the volume of infused solution (replacement solution plus circuit priming) into the blood compartment. When UF^{NET} is not null, patient fluid balance is negative after the treatment. For convective modalities, if the aim of the therapy is not to change the patient's fluid status, all the convective volume (i.e., UF^{TOT}), represented by priming volume plus replacement fluid volume, is returned to the patient during the session. When negative fluid balance is desired, UF^{TOT} is the priming volume, plus replacement fluid volume, plus the desired volume of negative fluid balance, the latter being UF^{NET}. For example, for a hemodiafiltration session in which UF^{NET} goal is 2 L, priming volume is 0.6 L, and replacement volume is programmed to be 21 L, the UF^{TOT} should be 23.6 L [18–21]. As noted, many clinicians erroneously utilize the terms UF^{TOT} and UF^{NET} interchangeably, which may lead to miscommunication and impact patient care. Thus, the following equations may be helpful:

UF^{TOT} = total fluid volume removed from the patient during the therapy (priming volume + replacement fluid volume + desired fluid removal volume from the patient)

UF^{NET} = balance of fluid volume removed from the patient (UF^{TOT} – priming volume – replacement fluid volume)

Adsorption

Adsorption is another method of extracorporeal clearance. It is described in detail below in the Materials section because it reflects, and is highly dependent on, membrane characteristics.

Clearance

Clearance (K) is the ratio of mass removal rate (N) to blood concentration (C_B):

$$K = N/C_B$$

For a dialysis filter, mass solute removal rate is the product of flow rate and solute concentration. Mass solute removal rate can be determined based on measurements derived from blood-based or effluent-based parameters. The general blood-side instantaneous clearance equation is

$$K_B = [(Q_{Bi} \cdot C_{Bi}) - (Q_{Bo} \cdot C_{Bo})] \div \{C_{Bi} + [Q_{UF}^{NET} \cdot (C_{Bo}/C_{Bi})]\}$$

K_B is the whole-blood clearance, Q_B is blood flow, C_B is whole-blood solute concentration, and $Q_{UF}{}^{NET}$ is UF^{NET} flow. The letters "i" and "o" represent the inlet and outlet of the blood filter, respectively. The difference between

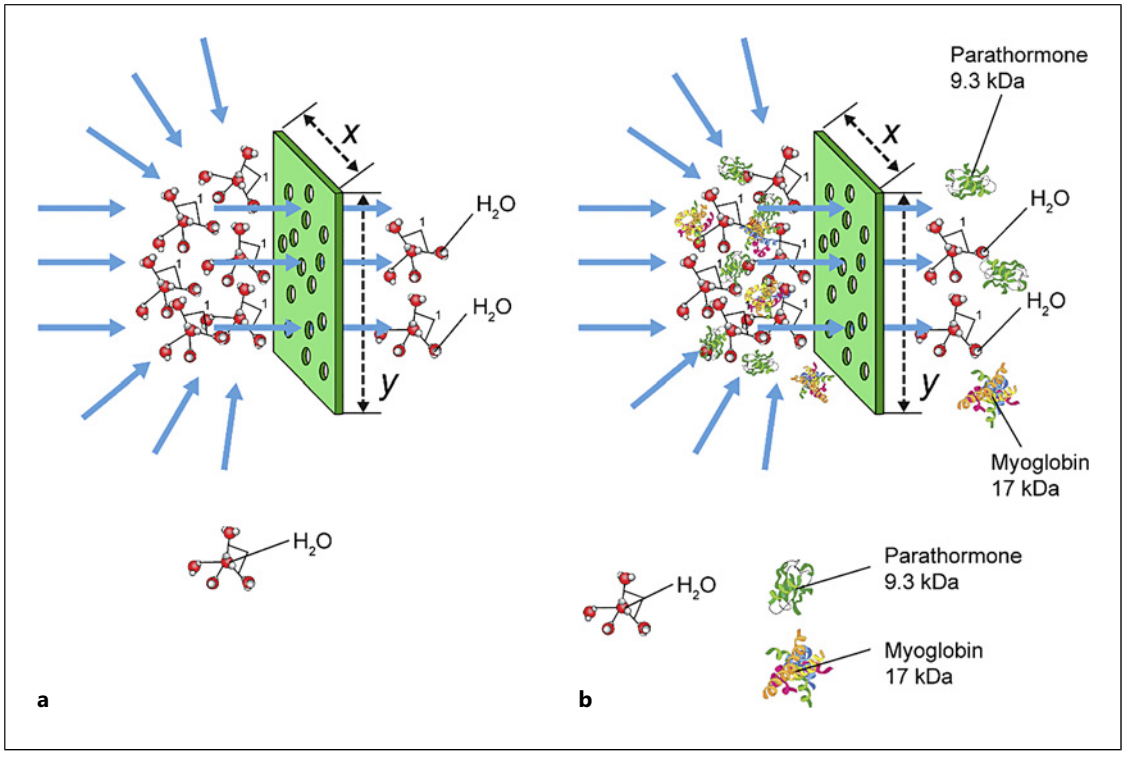

Fig. 3. Ultrafiltration and convection. **a** The arrows represent a pressure applied to water that forces it against a semipermeable membrane. The area of the membrane is the product of x · y. Some water molecules cross the membrane and the volume of water transferred over a specific time period represents the ultrafiltration flow (Q_{UF}). **b** Again, the arrows represent a pressure applied to a solution containing water and solutes that represents plasma. The area of the membrane is the product of x · y. The Q_{UF} is the driving force responsible for the convective transport of mass. Convective clearance is inversely proportional to molecule size. This is illustrated in the figure as a higher number of molecules of parathyroid hormone (9.3 kDa) that pass through the membrane in comparison to myoglobin (17 kDa). Therefore, the convective clearance is higher for parathormone than for myoglobin.

the rate of solute mass entering the filter and the rate of solute mass leaving the filter defines the mass removal rate of the filter. It should be noted that this equation is only relevant for conventional (intermittent) HD, in which large differences typically exist between inlet and outlet blood concentrations for solutes of interest.

For continuous renal replacement therapies (CRRTs), solute clearance likewise is the ratio of mass removal rate to blood concentration, but in this case, the former is estimated by the product of effluent solute concentration and flow at a given time (i.e., presumed to be instantaneous). Use of effluent parameters to estimate CRRT clearance is necessary due to its relatively low efficiency that does not result in large differences between filter inlet and outlet blood solute concentrations (as is the case for conventional HD). For example, if (prefilter) blood urea (nitrogen) concentration is 100 mg/dL, effluent urea concentration is 97 mg/dL, and effluent flow is 2,400 mL/h (i.e., 40 mL/min), urea clearance is 38.8 mL/min. Historically, with regard to effluent, some clinicians have preferred to use terminology specific to a given continuous modality (hemodialysis: dialysate; hemofiltration: filtrate; hemodiafiltration: diafiltrate). However, this approach creates confusion because these terms may not incorporate the net ultrafiltrate component of the therapy – as such, use of the generic term "effluent" is preferred.

Materials and Their Characteristics Utilized in Extracorporeal Blood Purification

Filter

The filter is a device consisting primarily of a bundle of semipermeable hollow fiber membranes surrounded by a plastic housing. Membrane characteristics having a significant impact on filter performance include length, inner diameter, wall thickness and structure, number of fibers (surface area), and composition of the fibers, along with the average size, density, and distribution of the pores. These characteristics determine the important

parameters used to characterize filter performance, including ultrafiltration coefficient (K_{UF}), mass transfer area coefficient (K_0A), sieving coefficient (SC), retention onset (RO), cutoff (CO), and adsorptive capacity. When describing filters used in extracorporeal therapies, these parameters should be identified and quantified. Specific aspects of membranes and filters are described below.

Membrane Composition

Membranes for extracorporeal renal replacement therapies are broadly divided into natural and synthetic fibers. The material for natural membranes is derived from cellulose, and unmodified cellulosic membranes were exclusively used in the earliest applications of HD [22]. Improvements in biocompatibility and depurative characteristics have been achieved over time with modified (semisynthetic) cellulose membranes, such as cellulose acetate, diacetate, and triacetate [12, 23–25]. However, utilization of such membranes for chronic renal replacement has decreased dramatically, and the vast majority of extracorporeal treatments now involve the use of synthetic membranes [26]. Most contemporary treatments incorporate filters comprised of PAES/PES (poly[aryl] ether sulfone]) [27], polysulfone [28], polyamide [29], PMMA (polymethylmethacrylate) [30], or acrylonitrile [31, 32] membranes. As described below, these filters are generally more biocompatible than cellulose-based filters.

Membrane Ultrafiltration Coefficient

Ultrafiltration coefficient (K_{UF}) represents the intrinsic permeability of the membrane to water. It is defined by the relationship between the volumetric rate of transmembrane solvent transfer (mL/h) and transmembrane pressure (mm Hg) for a given surface area (m^2) [33]. At relatively low transmembrane pressures, this relationship is linear, and K_{UF} is the slope:

$$K_{UF}\ (\mathrm{mL/h/mm\ Hg/m^2}) = Q_{UF}/\mathrm{TMP} \cdot 1/A$$

Based on this intrinsic membrane K_{UF}, the filter (device) ultrafiltration coefficient (DK_{UF}: mL/h/mm Hg) can be determined as the product of K_{UF} and membrane surface area (A):

$$DK_{UF} = K_{UF} \cdot A$$

Manufacturers provide filter K_{UF} values based on in vitro experiments in which bovine or human blood of known hematocrit and plasma protein concentration is ultrafiltered at a specific rate over a relevant TMP range (according to ISO 8637-1) [14].

Flux and Membrane Characteristics

The K_{UF} has been used historically to define "high-flux" or "low-flux" membranes. Although there is no definitive consensus in the literature regarding the K_{UF} CO value [34], it is generally assumed that a K_{UF} <15 mL/h/mm Hg/m^2 identifies a low-flux membrane, and K_{UF} ≥15 mL/h/mm Hg/m^2 identifies a high-flux membranes [33]. This only describes the hydraulic permeability of the membrane, which is highly correlated with mean pore size. While mean pore size is also an important determinant of the solute permeability of a membrane, other membrane characteristics also have an impact, including pore density and distribution. For this reason, the terms high-flux and highly permeable membrane are not interchangeable [34]. For the sake of clarity, the terms high or low ultrafiltration coefficient are more descriptive than the use of high or low flux.

Mass Transfer Area Coefficient

The mass transfer area coefficient (K_0A) represents the overall capacity of the filter to provide diffusive removal of a specific solute. K_0A is the theoretical maximum (diffusive) clearance of a filter for a given solute at infinite blood and dialysate flows. K_0 is defined as the ratio of solute flux (mass removal rate normalized to membrane surface area) to the transmembrane concentration gradient driving diffusive mass transfer. In turn, the concentration gradient reflects the three filter components (blood and dialysate compartments along with the membrane) that dictate overall diffusive mass transfer. Each of these components has an associated mass transfer "resistance" – the overall mass transfer resistance (R_0) is the sum of the three individual resistances and is the inverse of K_0 ($K_0 = 1/R_0$). The product of K_0 and filter surface area (A) has the same units as clearance (mL/min), consistent with K_0A's representation as a theoretically maximal clearance. The datasheet provided by filter manufacturers typically includes the K_0A values at least for urea and sometimes for other solutes. However, these values are based on in vitro data derived from experiments using aqueous solutions as "blood" substitutes and can substantially overestimate in vivo K_0A values. Moreover, membrane mass transfer resistance may increase during a treatment due to deposition of plasma proteins on the surface of the filter to form a "secondary membrane". While these factors influence the K_0 component of K_0A, changes in effective membrane surface area during a treatment may also mediate the difference between in vitro and in vivo K_0A values. Specifically, clotting or the collapse of some hollow fibers results in a loss of membrane surface area available for mass transfer [14].

Sieving Coefficient

The SC of unbound solutes reflects the size of the membrane pores in relation to the size of the molecule and is a measure of a molecule's ability to penetrate the membrane's pore structure [14]. Thus, the governing equation for SC is the ratio of the concentration of the solute in the ultrafiltrate (C_F) to the solute concentration in plasma water (C_P) in the absence of a diffusion gradient across the membrane [16]:

$$SC = C_F/C_P$$

The sieving coefficient is highly dependent on membrane mean pore size and is specific for a given solute/membrane combination. Sieving coefficient data provided by filter manufacturers are derived from in vitro standardized systems employing aqueous (protein-free) solutions. Analogous to the interpretation of K_0A data, clinical (in vivo) sieving coefficient values are typically lower than those provided by filter manufacturers and may decrease substantially during treatment due to secondary membrane effects [16].

RO and CO

RO and CO are intrinsic characteristics of a specific membrane. The RO for a specific membrane represents the molecular weight corresponding to a SC of 0.9, or a probability of 90% or less that a molecule has of fully permeating through the membrane. The CO for a specific membrane represents the molecular weight corresponding to a SC of 0.1, or a probability of 10% or less that a

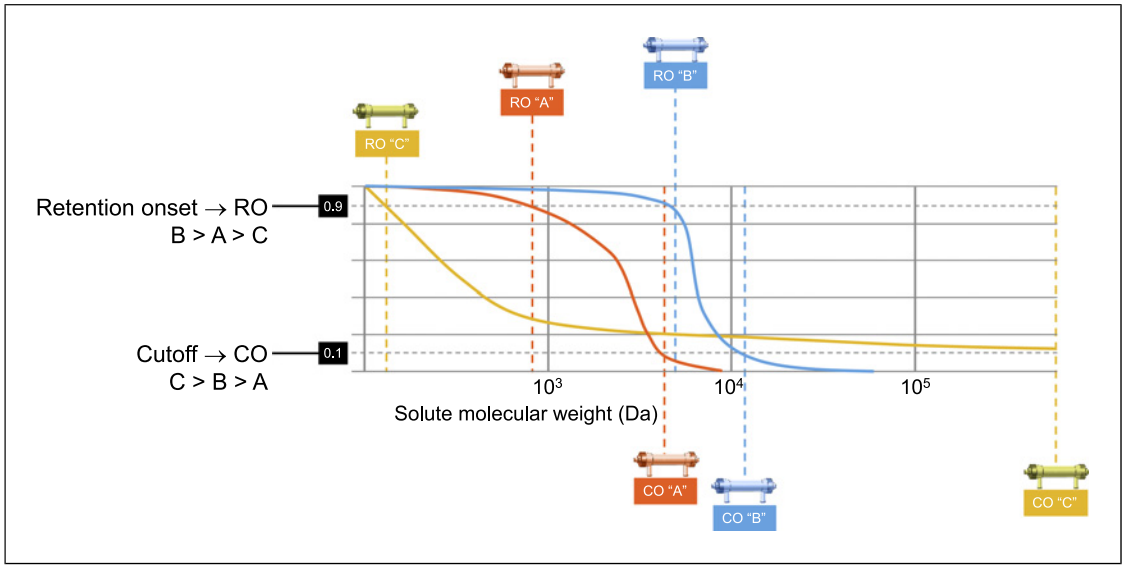

Fig. 4. Theoretical sieving curves of three membranes. The RO is the molecular weight at which the sieving coefficient reaches 0.9, while the CO is the molecular weight at which the sieving coefficient reaches 0.1. Membrane "C" has the lowest RO and solutes with lower molecular weight, such as small (<0.5 kDa) and small-middle (0.5–15 kDa) molecules, start to be retained first for membrane "C". Membrane "C" has the highest CO, far surpassing 68.000 Da, which is the molecular weight of albumin. A CO above this value is problematic since a significant amount of albumin loss can occur during the dialysis session. Membrane "B" has the highest RO, which is a desired characteristic because this parameter is correlated with increased removal of higher molecular weight uremic toxins. Membrane "B" also has the desirable characteristic of a CO lower than albumin's molecular weight. Lastly, membrane "A" has a lower RO than membrane "B" and a lower CO than membrane "B". Therefore, membrane "A" likely affords equal capacity to remove small molecules (<0.5 kDa) as membrane "B". However, for small-middle (0.5–15 kDa), medium-middle (>15–25 kDa), and large-middle (>25–58 kDa) molecules, membrane "B" is more efficacious. RO, retention onset; CO, cutoff.

molecule has of fully permeating through the membrane [17, 35, 36]. For a nuanced understanding of the performance characteristics of a membrane, the RO and the CO values provide a more precise representation of its capabilities because they delineate the molecular weight range of uremic toxins that can be cleared (Fig. 4). In contrast, the classification of membranes based solely on water permeability (i.e., K_{UF}, low- and high-flux) is unsatisfactory because of its inability to characterize a membrane's capabilities in this respect [34, 37].

Filtration Fraction

As blood is ultrafiltered, plasma water and dissolved solutes capable of permeating the membrane pore structure are removed while most proteins and all formed elements are retained. This results in progressive concentration of these retained components as blood flows axially (longitudinally) with resultant changes in blood and plasma viscosity. Filtration fraction (FF) is a measure of the extent to which this hemoconcentration occurs and is the ratio of the total UF^{TOT} to either the total blood flow (Q_B) or plasma flow (Q_P) delivered to the filter. With Q_P expressed as

$$Q_P = Q_B \cdot (1\text{–hematocrit})$$

FF can be defined as

$$FF = Q_{UF}^{TOT}/Q_P$$

While FF is a consideration for any convective therapy, it is most relevant for modalities involving post-filter delivery of replacement fluid as these generally are associated with the greatest degree of hemoconcentration. Practically, FF should not exceed 20–25% – higher FF corresponds to higher post-filter hematocrit, which promotes clot formation and degradation of filter performance.

Adsorption and Adsorptive Capacity

While transmembrane mechanisms (diffusion and/or convection) account for most solute clearance achieved by renal replacement modalities, membrane adsorption may be relevant for certain types of solutes. Some highly permeable membranes are capable of adsorbing uremic peptides and low molecular weight proteins in relatively large quantities. In fact, adsorption may be the predominant removal mechanism for such solutes by specific membranes (e.g., sulfonated polyacrylonitrile and polymethylmethacrylate). In addition to membrane material, available surface area for adsorption is an important consideration. In this regard, a prerequisite for clinically relevant adsorptive clearance of relatively large uremic solutes is access to the membrane internal pore structure, for which the effective surface area is vastly greater than that associated with the nominal (blood-contacting) surface. This necessarily implies that mean membrane pore size must be sufficiently large to allow such access. Although solute adsorptive clearance and overall adsorptive capacity for a given filter are not

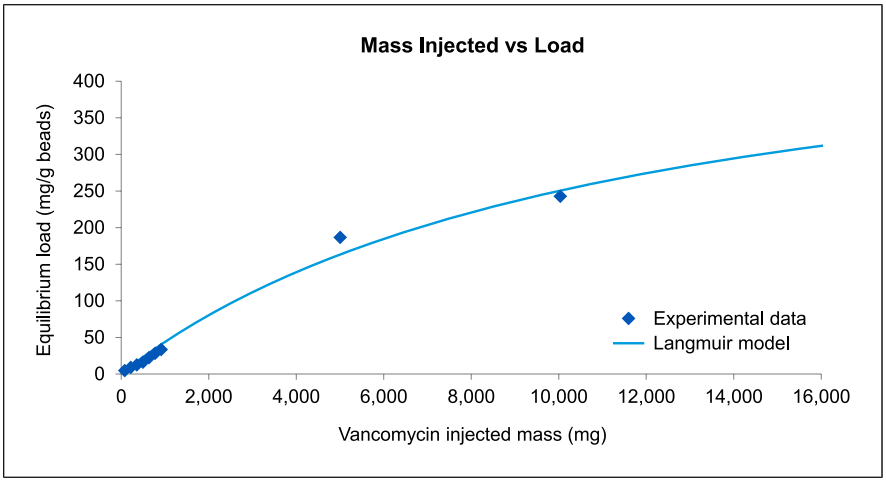

Fig. 5. Adsorption isotherm for vancomycin. This graphic represents an in vitro experiment in which vancomycin was added to a closed-loop circuit with saline solution continuously passing through a cartridge with sorbent material (resin beads). The independent variable was the injected mass of vancomycin; the dependent variable was the ratio between the mass of vancomycin adsorbed and the mass of the sorbent in the cartridge. The slope of the curve progressively diminishes to reach a plateau when the adsorptive sites are fully occupied, denoting sorbent saturation. Modified with permission from reference 38.

parameters routinely provided by manufacturers, multiple studies have demonstrated the importance of adsorption for both chronic and acute indications of renal replacement modalities.

While it is a generally non-specific process for membrane-based modalities, extracorporeal adsorption can also be utilized in a more specific manner for the relatively targeted removal of certain solutes or solute classes. Such molecules are typically cleared to a limited degree by membrane-based modalities – for these solutes, hemoadsorption (extraction from whole blood) or plasmadsorption (extraction from plasma) can be used. The fundamental basis for these therapies is the interaction between solutes dissolved in a liquid (blood or plasma: sorbate) and a solid (sorbent) – when this interaction occurs, adsorption proceeds.

Adsorption as a removal mechanism is fundamentally characterized by the adsorption isotherm (Fig. 5). The isotherm is the equilibrium relationship between the amount of adsorbed material and the concentration of the solute of interest, at constant temperature [38, 39].

Sorbents

For the purposes of extracorporeal blood purification, a sorbent is broadly defined as a material used to adsorb pathogenic solutes from blood or plasma in a process called hemoadsorption. Sorbents can be composed of natural (e.g., carbons) or synthetic materials (e.g., polymers) and can be prepared as beads, granules, flakes, fibers, spheres, or cylindrical pellets ranging from 50 μm to 1.2 cm [40]. They are characterized by a high surface area-to-mass ratio, varying from 300 to 1,200 m^2/g [41]. The adsorptive materials are contained in a plastic cartridge provided with ports for plasma/blood inflow and outflow and specific screens to avoid dissemination of particles into the circulation.

Sorbent-based devices should be characterized by the following: (a) chemical composition; (b) structure (beads, fibers, others); (c) solute affinity; (d) porosity; and (e) coatings. In addition, the sorbent device description should include (a) volume of the sorbent, (b) packing density, and (c) capacity/saturability. These characteristics dictate the blood or plasma flow through the device, along with the kinetic properties of solute mass transfer leading up to adsorption. From this perspective, for bead-based sorbent devices, bulk flow (outside the beads) and flow within the pores of the beads are important considerations and influence the rate at which solute reaches the binding sites within the beads by diffusion and/or convection. While other mechanisms, such as ionic or van der Waal forces, may play a role, hydrophobic binding is the main mechanism of solute removal for extracorporeal sorbent devices [42]. All of these aspects are incorporated into the design of different hemoadsorption devices, significantly affecting the clinical effects of adsorption-based extracorporeal blood purification and their indications.

Surface Modification versus Functionalization of Membranes

Surface modification of the membrane is a physical or chemical process incorporated into the polymerization process with the effect of altering membrane performance [43, 44]. Functionalization is a form of further modification that occurs after polymerization and imbues specific functional characteristics to the membrane. Heparin-grafted acrylonitrile membranes [32, 45–47] and vitamin E-coated polysulfone membranes [48–51] are examples of functionalized membranes.

Biocompatibility

Biocompatibility is broadly defined as the host response to a foreign material [52]. In the setting of extracorporeal blood purification therapies, the blood is exposed repeatedly to different types of foreign surfaces, including membranes, sorbents, tubing, and vascular access devices. Activation of several inflammatory pathways may occur in response to the interaction between such surfaces and the patient's blood or plasma. Thrombogenicity, complement activation, leukopenia, thrombocytopenia, and elevations of inflammatory biomarkers are all manifestations of biocompatibility related to extracorporeal devices [53–58]. Indeed, there is a spirited debate about the definition of biocompatibility, and it has been suggested that "biotolerability" is more suitable. According to Ratner, biotolerability is the ability of a material to reside in the body for long periods of time with only low degrees of inflammatory reaction [59].

Modalities of Renal Replacement Therapy

The following are definitions and descriptions of the most common forms of extracorporeal RRT which utilize the operating principles described above. While many hybrid forms of RRT have been described in the literature, this section focuses on the most commonly utilized forms of therapy and the mechanisms of blood purification (Table 2).

Hemodialysis

The main mechanism of solute removal in HD is diffusion, which is chiefly effective in the clearance of small solutes. HD involves the use of a filter in which blood and dialysate circulate counter-currently to maximize the efficiency of solute removal. A counter-current configuration allows for the average concentration gradient to be kept higher along the entire length of the filter. High-flux filters (defined above) permit achievement of some degree of convective transport that supplements diffusive clearance (see below) – this modality is called high-flux HD [60]. As an example, the (aqueous) in vitro sieving coefficient of a solute in the 10,000 Da range may approach 1.0 for a high-flux filter, while the sieving coefficient of the same solute is zero for a low-flux filter [6].

It is important to note that while the increased permeability of membranes used in high-flux HD allows for greater passage of large uremic toxins (relative to low-permeability membranes), their removal is still limited in two major ways. First, such solutes have low diffusivities, both in solution (blood and dialysate) but especially within membranes (even those having relatively large pore sizes). The second limiting factor is the low ultrafiltration flows used in HD, which are prescribed only to achieve the net fluid removal requirements of the patient. Nevertheless, the dominant mechanism by which large uremic toxins are cleared during high-flux HD is convection, as explained below.

For a high-flux dialyzer operated in the HD mode, a large axial pressure drop in the blood compartment results in significant variation in the net transmembrane pressure gradient along the length of the filter. While a blood-to-dialysate TMP gradient exists in the proximal segment of the filter, hydrostatic and osmotic pressure changes in the blood compartment lead to the development of a "reverse TMP" at the approximate mid-point, resulting in ultrafiltration from dialysate to blood ("backfiltration") in the distal filter segment. Thus, an "internal filtration" circuit, in which ultrafiltrate flows from blood to dialysate in the proximal segment and dialysate to blood in the distal segment, is established. This may result in proximal ultrafiltration flows as high as 80 mL/min. The convective solute removal occurring in association with this circuit is typically responsible for the majority of large solute elimination during high-flux HD. On the other hand, in HDF (see below), ultrafiltration occurs only from blood to dialysate along the entire length of the hollow fiber under typical operating conditions, so backfiltration is not a relevant consideration.

Hemofiltration

HF exclusively uses ultrafiltration to achieve convective solute clearance. Ultrafiltration flows far in excess of those required for the patient's net fluid removal requirements are prescribed in conjunction with filters having highly permeable membranes to enhance large toxin clearance relative to high-flux HD. An infusion of a sterile replacement fluid into the blood circuit reconstitutes the reduced plasma volume that results from the high ultrafiltration flows prescribed. Infusion of this replacement solution can replace totally or partially the filtered volume depending on the net fluid removal needs of the patient. Replacement fluid can be infused pre-filter or post-filter. In terms of solute clearance, post-filter is more efficient than pre-filter as the former does not reduce solute concentrations by dilution in the blood passing through the filter. However, pre-filter replacement solutions may preserve membrane performance and decrease clotting risk (by mitigating hemoconcentration and membrane fouling) [61]. It is worth noting that HF in the chronic setting has been abandoned due to its inability to provide sufficient small solute clearances.

Hemodiafiltration

HDF combines the processes of HD (diffusive clearance) and HF (convective clearance). It was developed initially as a chronic modality to overcome the limitations of HF related to small solute clearances while still having a significant convective component. This modality requires the use of high-flux membranes as well as high ultrafiltration flows. Fluid is removed by ultrafiltration, and the volume of filtered fluid exceeding the volume required to achieve target fluid weight loss is replaced by intravenous-quality infusion solution (as in HF). Online HDF refers to the real-time production by the dialysis machine of nearly unlimited volumes of ultrapure, nonpyrogenic dialysate, which is processed further to produce an infusion (replacement) fluid. High-volume HDF is defined by an effective convection volume of at least 20% of the total blood volume processed.

As is the case in HF, post-filter HDF is most efficient in terms of solute removal but is limited by hemoconcentration (i.e., filtration fraction). On the other hand, although ultrafiltration flow up to 100% of blood flow is

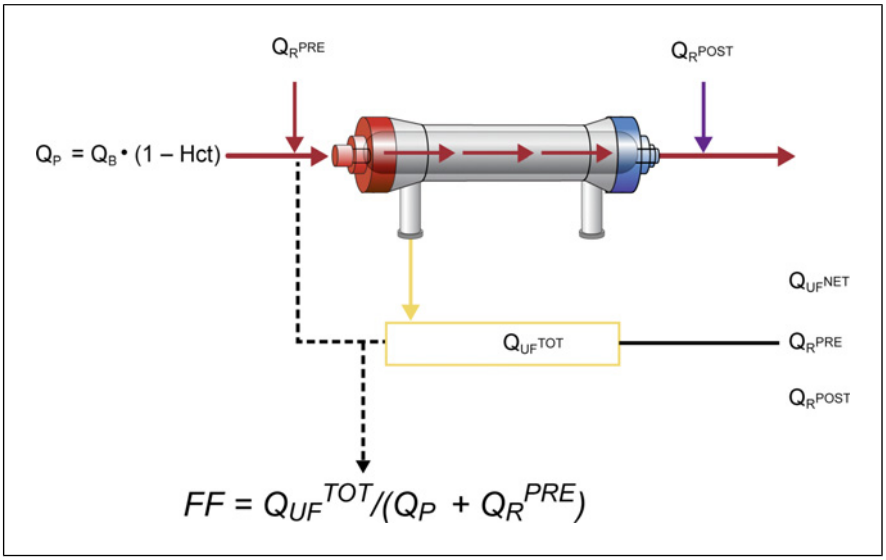

Fig. 6. Determinants of FF (filtration fraction). Htc, hematocrit; Q_B, blood flow; Q_P, plasma flow; Q_R^{POST}, post-filter replacement flow; Q_R^{PRE}, prefilter replacement flow; Q_{UF}^{NET}, net ultrafiltration flow; Q_{UF}^{TOT}, total ultrafiltration flow.

possible in pre-filter HDF, the efficiency of this mode is much lower than post-filter HDF because of the dilution-related reduction of solute blood concentrations, reducing both diffusive and convective removal rates. The latter can only be overcome by the use of very high ultrafiltration (and, therefore, replacement fluid) flows [62].

FF is a key consideration in convective therapies, especially those delivered in the post-filter mode. In convective CRRTs such as continuous veno-venous hemofiltration (CVVH) and continuous veno-venous HDF (CVVHDF) with post-filter replacement, FF should be kept below 20% [63] (Fig. 6). Likewise, in intermittent convective modalities used with post-filter replacement (HDF or HF), FF above 30% is not recommended.

Isolated Ultrafiltration

Isolated ultrafiltration removes fluid using semipermeable membranes without volume replacement, thus achieving net volume but not net solute removal in the patient. This technique has obvious advantages for clinical scenarios of volume overload refractory to medical management but where control of electrolyte, acid-base, or other abnormalities that would be treated with dialysis is not critical [64–69].

Plasmapheresis describes the process in which plasma is selectively removed after separation from blood cells and is normally replaced with plasma-derived products, such as fresh frozen plasma, albumin, or other fluids. Typically, plasmapheresis is used to remove high molecular weight pathogenic proteins (such as antibodies or abnormal plasma proteins) or protein-bound substances not effectively removed by conventional dialysis therapies. It can be either performed with a selective plasma filter or alternatively, plasma can be extracted gravimetrically from whole blood using a centrifuge pump.

When therapeutic plasmapheresis is performed with a centrifugal machine, the principle of gravity sedimentation is utilized. In centrifugation, a rotor spins a solution contained in a chamber around an axis (centrifuge rotor) at high speed, creating a gravitational force. This unit compares the acceleration due to centrifugation to the acceleration caused by Earth's gravity. According to the difference densities of the substances, those with higher densities sediment first in the periphery of the chamber, separating the substances into strata [70].

Hemo- or Plasmadsorption

Hemo- or plasmaadsorption refers to the circulation of blood or plasma, respectively, through a device containing specific sorbents, with adsorption as the only mechanism for removal of specific solutes or substances. Usually combined with other modalities, hemoadsorption and plasmadsorption are used to remove specific hydrophobic (lipid-soluble) substances, toxins, or poisons.

Dose of Dialysis Therapies

Dialysis dose is defined in various ways depending on the modality used. Studies in the general adult population have demonstrated a direct relationship between dose and survival for both intermittent and CRRT modalities up to maximal level beyond which there is no further benefit.

In maintenance dialysis therapies, dose identifies the volume of blood cleared of urea from the body per unit of time. Clinical practice for maintenance dialysis involves use of a treatment clearance derived from blood solute concentrations measured before and after a session (reduction ratio) – this is the basis for urea Kt/V determinations in this modality, where K is urea clearance unit: volume/time), t is the duration of treatment, and V is the urea distribution volume. Note this differs from the previously described filter clearance, which utilizes instantaneous measurements of inlet and outlet blood solute concentrations. When using CRRT to treat critically ill patients, other measures of adequacy and dose should also be considered. The clinical dose standard here is not based on clearance of a specific solute but rather on daily treatment effluent volume.

One potentially easier and more reproducible means of estimating dose is incorporating the measurement of flow provided by the dialysis machine. The target dose (prescribed) is the clearance prescribed for a specific patient in his/her specific clinical condition and represents the clearance the prescribing clinician wants to achieve in that patient. The target machine dose is the clearance that the prescribing clinician wants to achieve from the machine. It is usually set as a target machine efficiency or by specifying the flow settings and RRT modality. The target machine dose can be modified during the treatment to reduce the mismatch between the target dose (prescribed) and the average effective delivered dose (measured). The average dose (measured/calculated) is the clearance calculated for the current dose applied over the total treatment time. The total time of treatment is defined as the sum of the effective time of treatment and downtime. The effective time of treatment is the cumulative time during which the effluent pump is operating. The average dose is usually an overestimate of the average effective delivered dose.

Pediatric Considerations

In pediatric patients, dose is corrected for body surface area. Particular attention must be paid to the priming volume required for the dialysis circuit, and if the volume exceeds 10% of blood volume, blood priming is warranted. Furthermore, the effects of dialysis dose on nutrition in growing children are incompletely understood and under investigation.

Conclusion

Consistent and clear terminology allows for direct communication that facilitates patient safety, allows for comparison of therapies along with outcomes, and creates a standard that aids the advancement of new technologies. This paper describes the development of standardized terminology for both the materials and methods utilized in extracorporeal therapies. These definitions create a common platform for utilization of these materials and methodologies in patient care. Subsequent papers from the conference discuss these uses in kidney failure and acute disorders, including acute kidney injury, heart failure, trauma, and sepsis.

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Statement of Ethics

Details have been given in ICJME disclosure form.

Conflict of Interest Statement

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