The Biology of Dialysis

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William R. Clark and Claudio Ronco

Introduction

Dialysis forms the cornerstone of therapy for most patients with chronic kidney disease Stage V (end-stage renal disease; ESRD) and many patients with acute kidney injury (AKI). Consequently, it is imperative that clinicians managing these patients understand the fundamental principles of dialytic therapies, especially those having a biologic basis. In this chapter, many of these principles are reviewed. The topic of uremic toxicity is first addressed, with emphasis on the classification of uremic toxins based on solute molecular weight (MW) and chemical characteristics. The dialytic solute removal mechanisms (diffusion, convection, and adsorption) broadly applicable to all renal replacement therapies are subsequently reviewed. As the major determinant of overall efficiency of hemodialysis (HD), the most commonly applied renal replacement therapy, diffusive solute removal will be rigorously assessed by applying a "resistance-in-series" model to a dialyzer. Moreover, new perspectives on the importance of specific membrane characteristics, including pore size and fiber inner diameter, will be discussed. In much the same way, fluid and mass transfer in peritoneal dialysis will be assessed by examining the elements of the system: peritoneal microcirculation, peritoneal membrane, and the dialysate compartment. Finally, from a kinetic perspective, the differences between intermittent, continuous, and semi-continuous therapies will be discussed, with emphasis on quantification of solute removal.

W. R. Clark (✉)
Department of Chemical Engineering, Purdue University, West Lafayette, IN, USA
e-mail: clarkw@purdue.edu

C. Ronco
Department of Medicine, University of Padova, Padova, Italy

Department of Nephrology Dialysis and Transplantation, International Renal Research Institute (IRRIV), San Bortolo Hospital, Vicenza, Italy
e-mail: cronco@goldnet.it

Biology of Uremic Toxicity

One of the major functions of the kidney is to eliminate waste products and toxins generated from a variety of metabolic processes [1]. Normal kidney function provides efficient elimination of these solutes, allowing for control of their blood and tissue concentrations at relatively low levels. On the other hand, toxin retention is felt to be a major contributor to the development of uremia in patients with advanced chronic kidney disease and ESRD [2].

In the classic taxonomy, uremic retention compounds are divided into three categories [3]: small solutes, "middle molecules," and protein-bound toxins. Compounds comprising the first category, for which the upper molecular weight limit is generally considered to be 500 Da, possess a high degree of water solubility and minimal or absent protein binding [4]. Despite having

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significant kinetic differences, both urea and creatinine are considered to be representative molecules (surrogates) for the small solute class. Nevertheless, as discussed below, it remains a matter of debate whether these two solutes themselves are toxic per se.

The second category of middle molecules has largely evolved now to be synonymous with peptides and proteins that accumulate in uremia [5]. Although not precisely defined, low molecular weight proteins (LMWP) as a class have a molecular weight spectrum ranging from approximately 500 to 60,000 daltons [6]. Thus, peptides with as few as ten amino acids and proteins nearly as large as albumin comprise this group. In patients with intact kidney function, these compounds are initially filtered by the glomerulus and subsequently undergo catabolism with reclamation of the constituent amino acids at the level of the proximal tubule [7, 8]. While the kidney is not the sole organ responsible for detoxification of these compounds, renal elimination accounts for 30–80% of total metabolic removal.

The final category of uremic retention compounds, one which has received much less attention than the other two, is protein-bound uremic toxins (PBUTs) [9, 10]. As opposed to the above small, highly water-soluble toxins, which are largely by-products of protein metabolism, PBUTs have diverse origins and possess chemical characteristics that preclude the possibility of circulation in an unbound form despite being of low molecular weight (<500 daltons also). These organic molecules typically have ionic and/or hydrophobic characteristics and bind avidly to albumin in the blood. Under conditions of normal kidney function, they are eliminated primarily by organic acid transporters (OATs) residing in the proximal tubule [11, 12]. Uremia is associated with elevated concentrations of both bound and unbound forms of PBUTs, with both reduced renal elimination and impaired albumin binding considered to be important factors [13]. Attention has focused on the metabolic products of the gut microbiome as the source of many PBUTs, including indoxyl sulfate and *p*-cresol [14, 15] (Fig. 2.1). The general topic of uremic toxicity

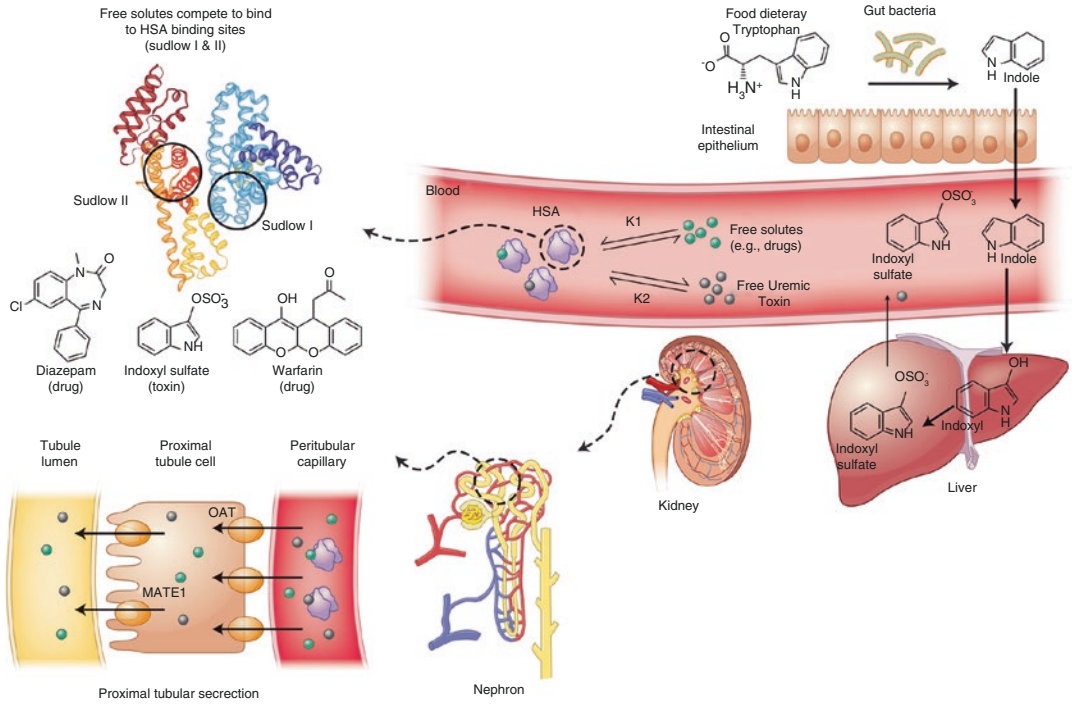

Fig. 2.1 Generation and elimination of gut-derived protein-bound uremic toxins. (Modified from Clark et al. (2019) [15])

has been comprehensively assessed in a recent review by Clark et al. [15].

Solute Removal Mechanisms in Extracorporeal Dialysis

Diffusion

Diffusion involves the mass transfer of a solute in response to a concentration gradient. The inherent rate of diffusion of a solute is termed its diffusivity [16], whether this in solution (such as dialysate and blood) or within an extracorporeal membrane. Diffusivity in solution is inversely proportional to solute MW and directly proportional to solution temperature [17]. Solute diffusion within a membrane is influenced by both membrane thickness (diffusion path length) and membrane diffusivity [18], which is a function of both pore size and number (density).

In hemodialysis (HD), the overall mass transfer coefficient-area product (KoA) is used to quantify the diffusion characteristics of a particular solute–membrane combination under a defined set of operating conditions [19]. The overall mass transfer coefficient is the inverse of the overall resistance to diffusive mass transfer, the latter being a more applicable quantitative parameter from an engineering perspective:

$$K_O = 1/R_O \tag{2.1}$$

The overall mass transfer resistance can be viewed as the sum of resistances in series [20]:

$$R_O = R_B + R_M + R_D \tag{2.2}$$

where R_B, R_M, and R_D are the mass transfer resistances associated with the blood, membrane, and dialysate, respectively. In turn, each resistance component is a function of both diffusion path length (x) and diffusivity (D):

$$R_O = (x/D)_B + (x/D)_M + (x/D)_D \tag{2.3}$$

The diffusive mass transfer resistance of both the blood and dialysate compartments for a hemodialyzer is primarily due to the unstirred (boundary) layer just adjacent to the membrane [21, 22]. Minimizing the thickness of these unstirred layers is primarily dependent on achieving relatively high shear rates, particularly in the blood compartment [23]. For similar blood flow rates, higher blood compartment shear rates are achieved with a hollow fiber dialyzer than a flat plate dialyzer. Indeed, based on the blood and dialysate flow rates (generally at least 250 and 500 mL/min, respectively) achieved in contemporary HD with hollow fiber dialyzers, the controlling diffusive resistance for solutes larger than approximately 200 daltons is that due to the membrane itself [24] (Fig. 2.2).

Another approach to quantifying diffusive mass transfer specifically through an extracorporeal membrane is by use of Fick's law of diffusion [25]:

$$N = D \cdot A(\Delta C/\Delta x) \tag{2.4}$$

where D is the solute diffusivity (area/time), A is the membrane area, ΔC is the transmembrane concentration gradient, and Δx is the diffusion path length. With increasing solute molecular weight, pore size limitations become increasingly important in restricting solute entry and limiting ("hindering") diffusion of molecules that gain pore entry [26, 27]. Thus, for a given concentration gradient across a membrane, the rate of diffusive solute removal is directly proportional to

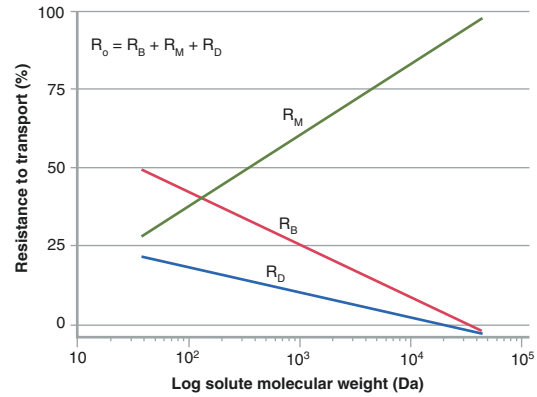

Fig. 2.2 Diffusive mass transfer resistances in a hemodialyzer. (Modified from Ronco and Clark (2018) [24])

the membrane diffusivity and indirectly proportional to the effective thickness of the membrane.

Membrane diffusivity is determined both by the pore size distribution and by the number of pores per unit membrane area (pore density). Based on a model in which a membrane has N (straight) cylindrical pores (per unit membrane surface area) of radius r oriented perpendicular to the flow of blood and dialysate, diffusive solute flux (φ: mass removal rate per unit membrane surface area) can be expressed as [28]:

$$\varphi = \lambda D \rho \Delta C / t \tag{2.5}$$

where λ is the solute partition coefficient, D is solute diffusivity, ρ is membrane porosity, ΔC is the transmembrane concentration gradient, and t is membrane thickness. (While the partition coefficient is essentially unity for solutes such as urea and creatinine, larger solutes with incomplete access to the membrane pores have λ values that are less than one.) Membrane porosity is a function of both pore size and number:

$$\rho = N \pi r^2 \tag{2.6}$$

Equations (2.5) and (2.6) suggest diffusive transport is relatively favorable for low molecular weight (LMW) solutes, due not only to the inverse relationship between MW and diffusivity but also to the greater access of small solutes to the membrane pore structure. Equation (2.5) also indicates diffusive transport is enhanced at low values of membrane thickness.

Diffusive mass transfer rates within a membrane decrease as solute MW increases not only due to effect of molecular size itself but also due to the resistance provided by the membrane pores. The difference in mean pore sizes between low-permeability dialysis membranes (e.g., regenerated cellulose) and high-permeability membranes (e.g., polysulfone, polyacrylonitrile, polyethersulfone) has a relatively small impact on small solute (urea, creatinine) diffusivities. This is related to the fact that even low-permeability membranes have pore sizes that are significantly larger than the molecular sizes of these solutes. However, as solute MW increases, the tight pore structure of the low-permeability membranes plays an increasingly constraining role such that diffusive removal of solutes larger than 1000 daltons is minimal by these membranes. On the other hand, the larger pore sizes which characterize high-flux membranes account for their higher diffusive permeabilities. Nevertheless, as discussed subsequently, the relatively limited ability of conventional high-flux membranes to remove large MW toxins due to pore size restrictions has generated interest in the use of membranes with larger pore dimensions.

Solute Removal by Convection

Convective solute removal is primarily determined by the sieving properties of the membrane used and the ultrafiltration rate [29]. The mechanism by which convection occurs is termed solvent drag. If the molecular dimensions of a solute are such that some degree of membrane permeation can occur, the solute is swept ("dragged") across the membrane in association with ultrafiltered plasma water. Thus, the rate of convective solute removal can be modified either by changes in the rate of solvent (plasma water) flow or in the mean effective pore size of the membrane.

Hydraulic flux (water permeability), the most common criterion traditionally used to classify dialysis membranes [16], is an important determinant of convective solute removal. The clinical parameter used to quantify water permeability is the ultrafiltration coefficient (Kuf), which is derived from the relationship between ultrafiltration rate (Qf) and TMP over a clinically relevant range of TMP. As suggested previously, a common first-order approximation of dialysis membrane pore structure is to assume that all pores are parallel and have the same radius, which results in ultrafiltrate flow that is perpendicular to the flow of blood and dialysate [30]. According to the Hagen–Poiseuille law [31], the rate of ultrafiltrate flow is proportional to the fourth power of the pore radius (i.e., r^4) at constant TMP. Thus, the membrane parameters that have the most substantial influence on water flux are the average

pore size and, to a lesser extent, the pore density per unit surface area.

The sieving coefficient is classically used to define the convective transport properties of a membrane for a specific solute. In Eq. (2.7), the sieving coefficient (SC) is the ratio between the solute concentration in the filtrate (Cf) and the solute concentration in the plasma water (Cp) [25, 29]:

$$SC = Cf / Cp \tag{2.7}$$

The observed (measured) SC values are influenced by interactions between the membrane and blood elements during dialysis. The nonspecific adsorption of a plasma protein layer, variously known as the secondary membrane, gel, or protein cake, reduces effective membrane permeability immediately upon exposure to blood [32–35] in a process known as fouling. In the convective removal of specific solutes, the influence of secondary membrane formation is directly proportional to solute molecular weight. The proteins found in the highest concentrations in the plasma, such as albumin, fibrinogen, and immunoglobulins, are the predominant components of the secondary membrane. This layer of proteins, by serving as an additional resistance to mass transfer, effectively reduces both the water and solute permeability of an extracorporeal membrane. Evidence of this is found in comparisons of solute sieving coefficients determined before and after exposure of a membrane to plasma or other protein-containing solution [36]. In general, the extent of secondary membrane development and its effect on membrane permeability is directly proportional to the membrane's adsorptive tendencies (i.e., hydrophobicity). Therefore, this process tends to be most evident for high-flux synthetic membranes, such as polysulfone and polymethylmethacrylate.

Both the water and solute permeability of a membrane used for therapies which involve relatively high ultrafiltration rates are influenced not only by secondary membrane formation but also concentration polarization [29] (Fig. 2.3). Although concentration polarization primarily pertains to plasma proteins, it is distinct from secondary membrane formation. Concentration polarization specifically relates to ultrafiltration-based processes and applies to the kinetic behavior of an individual protein. Accumulation of a plasma protein that is predominantly or completely rejected by a membrane used for ultrafiltration of plasma occurs at the blood compartment membrane surface. This surface accumulation causes the protein concentration just adjacent to the membrane surface (i.e., the submembranous concentration) to be higher than the bulk (plasma) concentration. In this manner, a submembranous (high) to bulk (low) concen-

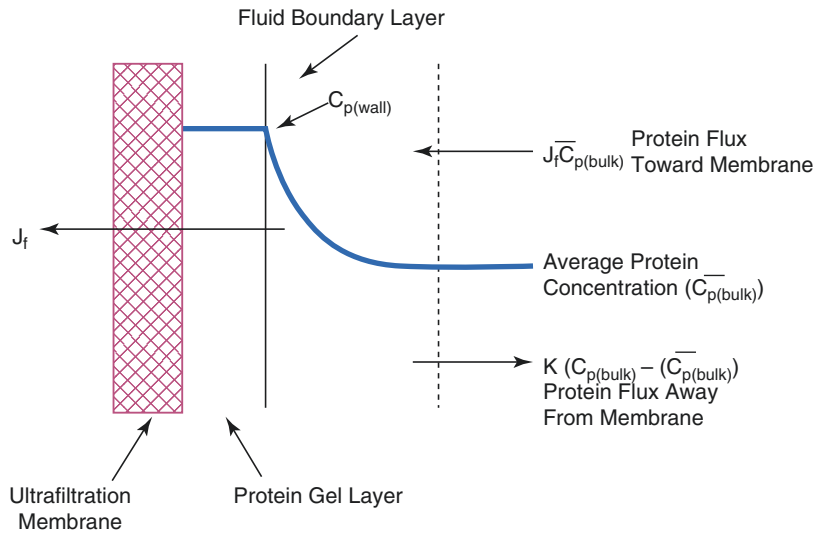

Fig. 2.3 Secondary membrane and concentration polarization phenomena in convective therapies. The protein gel layer corresponds to the secondary membrane while the fluid boundary layer represents concentration polarization. (Modified from Henderson (1996) [29])

tration gradient is established, resulting in "backdiffusion" from the membrane surface out into the plasma. At steady state, the rate of convective transport to the membrane surface is equal to the rate of backdiffusion. The polarized layer of protein is the distance defined by the gradient between the submembranous and bulk concentrations. This distance (or thickness) of the polarized layer, which can be estimated by mass balance techniques, reflects the extent of the concentration polarization process.

Conditions which promote concentration polarization are high ultrafiltration rate (high rate of convective transport), low blood flow rate (low shear rate), and the use of post-dilution (rather than pre-dilution) replacement fluids (increased local protein concentrations) [37]. By definition, concentration polarization is applicable in clinical situations in which relatively high ultrafiltration rates are used. Therefore, in the chronic dialysis setting, this phenomenon is potentially important in convective therapies (hemofiltration and hemodiafiltration).

The extent of the concentration polarization process determines its effect on actual solute (protein) removal. In general, the degree to which the removal of a protein is influenced correlates directly with that protein's extent of rejection by a particular membrane. In fact, concentration polarization actually enhances the removal of a MW class of proteins (30,000–70,000 daltons) that otherwise would have minimal convective removal. This is explained by the fact that the pertinent blood compartment concentration subjected to the ultrafiltrate flux is the high submembranous concentration primarily rather than the much lower bulk concentration. Therefore, the potentially desirable removal of certain proteins in this size range (e.g., β2M in ESRD patients) has to be weighed against the undesirable increase in convective albumin losses.

On the other hand, the use of very high ultrafiltration rates in conjunction with other conditions favorable to protein polarization may significantly impair overall membrane performance. The relationship between ultrafiltration rate and transmembrane pressure (TMP) is linear for relatively low ultrafiltration rates, and the positive slope of this line defines the ultrafiltration coefficient of the membrane. However, as ultrafiltration rate further increases, this curve eventually plateaus [38]. At this point, maintenance of a certain ultrafiltration rate is only achieved by a concomitant increase in TMP. At sufficiently high TMP, gelling of the membrane with denatured proteins may occur, and an irreversible decline in solute and water permeability of the membrane ensues. Therefore, the ultrafiltration rate (and associated TMP) used for a convective therapy with a specific membrane needs to fall on the initial (linear) portion of the UFR vs. TMP relationship with avoidance of the plateau region.

Solute Removal by Internal Filtration

Conventional membranes that are used in hemodialysis generally provide high clearance rates for small solutes such as urea and creatinine, irrespective of flux. However, membranes in current use, even those that are traditionally considered to be highly permeable, provide limited clearance of compounds >10 kDa for several reasons. Although these membranes have relatively large mean pore sizes (at least in comparison to unmodified cellulosic membranes), they still offer substantial mass transfer resistance to the diffusive removal of large solutes. Furthermore, fouling has a considerable effect on convective solute clearances, especially for molecules >10 kDa [35]. These constraints are particularly relevant in conditions involving high ultrafiltration rates, which promote secondary membrane formation by more effectively delivering plasma proteins to the membrane surface through convection (versus lower ultrafiltration rates). In typical hemodialysis operating conditions, the water permeability characteristics for a standard high-flux dialyzer result in a fairly large drop in the blood compartment axial (i.e., arterial end to venous end) pressure during treatment. The pressure drop is sufficiently

large that, at some point along the length of the dialyzer, the blood compartment pressure is less than the dialysate compartment pressure in normal operating conditions. Thus, especially considering the oncotic effects of plasma proteins in the blood compartment, there is a point at which the ultrafiltrate begins to be driven from the dialysate to the blood, as opposed to the "standard" (blood–dialysate) direction in the more proximal part of the dialyzer (Fig. 2.4). In fact, this combination of filtration and "backfiltration" [39–41] is considered to be the predominant mechanism by which larger compounds are removed during standard high-flux hemodialysis [42, 43], as explained further below.

The concentration of a molecule that is removed from the blood by convection in the proximal part of a high-flux dialyzer is substantially reduced once it crosses the membrane owing to the combination of sieving and the diluting effect of dialysate flow. When a portion of the dialysate is reinfused back into the blood as backfiltrate in the distal segment of the dialyzer, the amount of solute reinfused by solvent drag is negligible compared with that removed in the proximal part of the dialyzer owing to the blood–dialysate concentration difference, even if the filtration and backfiltration rates are similar. In fact, the reinfused fluid can be considered an "internal" substitution fluid because the concentration of the solute of interest is essentially zero. As such, in the context of high-flux hemodialysis, this mechanism has been termed "internal hemodiafiltration" or, more commonly, internal filtration. Maximizing the extent of internal filtration during high-flux hemodialysis through a combination of increased membrane permeability (increased pore size) and higher axial blood compartment resistance (decreased hollow fiber inner diameter) (44–46; see below) can provide clinically meaningful increases in large solute clearance. Internal filtration rates are estimated to be as high as 60 ml/min (~3.5 l/h) [40], and new membrane designs may be able to extend this range. However, strict control of dialysate quality is clearly of paramount importance in high-flux hemodialysis, especially when using such membranes.

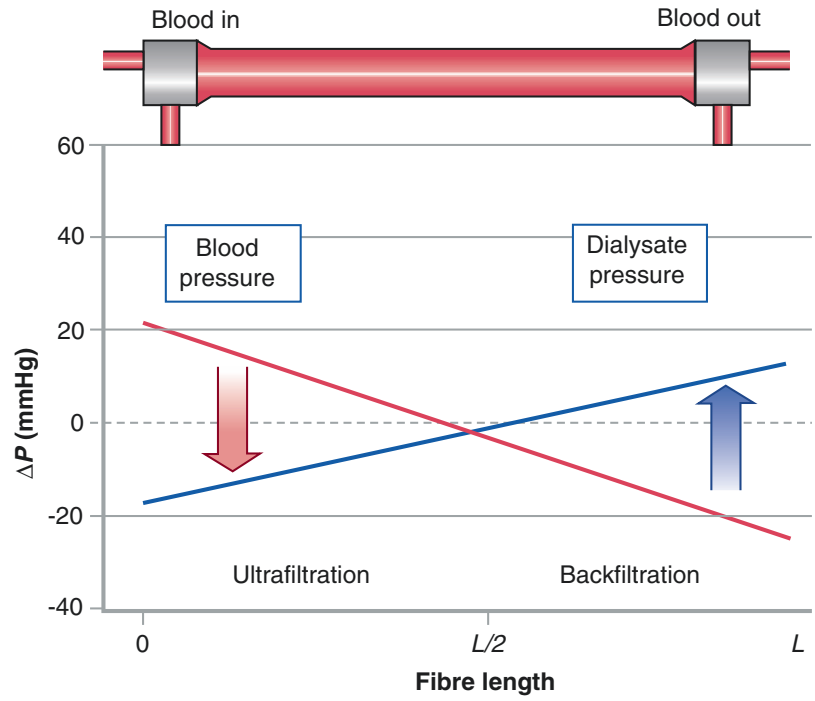

Fig. 2.4 Concept of internal filtration. (Modified from Ronco and Clark (2018) [24])

New Membrane Designs for Enhanced Removal of Large Toxins

While dialyzer classification has been based traditionally on water permeability (flux), new schemes that focus more on solute permeability properties have been proposed. These new classification systems acknowledge the importance of larger MW uremic toxins and the need to incorporate additional membrane classes that have extended removal spectra. High-flux and "protein-leaking" membranes have been defined on the basis of a combination of water permeability, β2m removal parameters (sieving coefficient or clearance), and albumin parameters (sieving coefficient or amount removed) [47]. In this system, the high-flux class is defined by a water permeability of 20–40 ml/h/mmHg/m^2, a β2m SC of 0.7–0.8, and albumin loss of <0.5 g (on the basis of a 4 h hemodialysis treatment), whereas the same parameters defining a protein-leaking membrane are >40 m/h/mmHg/m^2, 0.9–1.0, and 2–6 g, respectively. Although not explicitly stated, the Kuf and β2m SC values correspond to "virgin" membrane performance and do not reflect potential diminutions during treatment as a result of secondary membrane effects. Two new membrane classes, medium cut-off (MCO) and high cut-off (HCO), have been proposed, extending the earlier classification scheme [24]. The HCO class is characterized by a substantial increase in water permeability (relative to both the high-flux and the protein-leaking classes) and a virgin β2m SC of 1.0 [48]. However, the high albumin loss rates associated with this membrane class generally preclude their long-term use for patients with ESRD [49].

Thus, the design challenge is to maximize the removal of large uremic toxins while also maintaining albumin losses in a clinically acceptable range for long-term treatment of patients with ESRD. MCO membranes incorporate high-retention onset (HRO) properties, and this class may hold promise in addressing the challenge of achieving acceptable albumin losses. In comparison to HCO membranes, the MCO class is intended to preserve the β2m sieving characteristics and to improve the clearance of other large molecular weight solutes (e.g., free antibody light chains) while demonstrating a marked reduction in albumin permeability (Fig. 2.5).

Solute Removal by Adsorption

For certain HD membranes, adsorption (binding) may be the dominant or sole mechanism by which some hydrophobic compounds (e.g., peptides

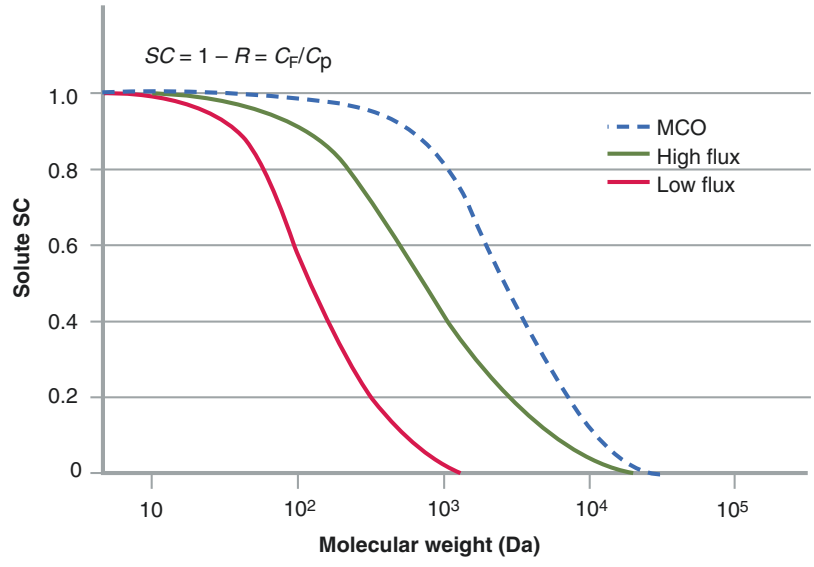

Fig. 2.5 Sieving coefficient curves for low-flux, standard high-flux, and medium cut-off (MCO) dialyzers. (Modified from Ronco and Clark (2018) [24])

and proteins) are removed [50–52]. The adsorptive surface area of a membrane resides primarily in the pore structure rather than the nominal surface area. As such, the adsorption of a LMW protein is highly dependent on access of the protein to a membrane's internal pore structure [53]. Consequently, adsorption of peptides and LMW proteins, such as β2M, to low-flux membranes is not expected to be clinically significant, at least in comparison to that which occurs to high-flux membranes. The adsorption affinity of certain high-flux synthetic membranes for proteins and peptides is particularly high, generally attributable to the relative hydrophobicity of these membranes [54].

Peritoneal Dialysis: Biologic and Mass Transfer Considerations

The peritoneal dialysis system has three major components: (1) the peritoneal microcirculation, (2) the peritoneal membrane, and (3) the dialysate compartment that includes the composition of the solution and the modalities of delivery. All these three components may have an important impact on the final performance of the technique [55].

Factors Affecting Solute Transport

The Dialysate Compartment In Fig. 2.6, urea clearance is plotted against dialysate flow rate. The curve identifies three specific regions. The first region includes the dialysate flow rates typical for continuous ambulatory peritoneal dialysis (CAPD) involving three to five exchanges/day. In this region, the correlation is very steep, and clearance displays significant changes even in response to minimal changes in the dialysate flow. This region is therefore dialysate flow dependent or flow limited, since the volume of the dialysate per day is the factor that chiefly limits the clearance value. In this region, it would be simple theoretically to increase the dialysate flow by a few mL/day to achieve much higher clearances and, consequently, significant increases in Kt/V. However, while theoretically possible this would not be feasible in practice since it would mean carrying out six to ten exchanges/day. Therefore, a typical CAPD technique is basically dialysate flow limited. The only possible way to increase the dialysate flow without increasing the number of exchanges is to increase the volume of solution per exchange.

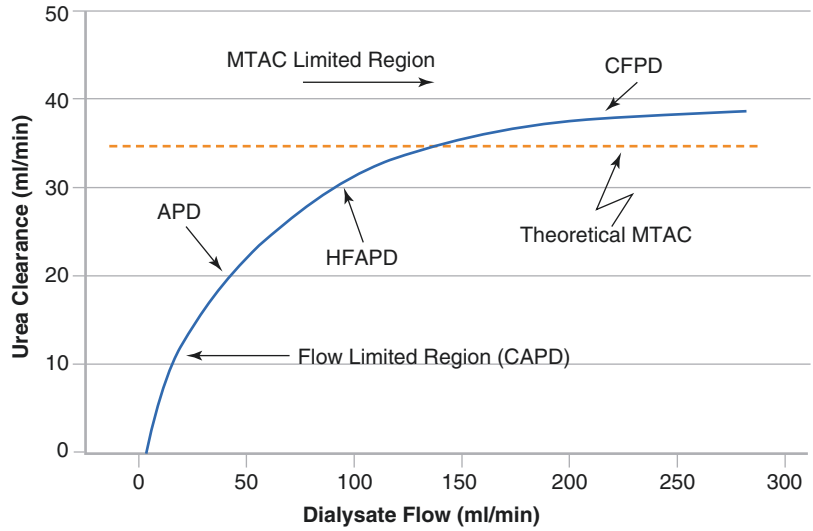

Fig. 2.6 Plot of urea clearance vs. dialysate flow rate in peritoneal dialysis. (Modified from Ronco and Clark (2001) [17])

The second part of the curve is the typical region of automated or intermittent peritoneal dialysis. The dialysate flows may vary significantly due to a variation of the dwell time (from 30 min to 0) and on the number of exchanges per day. Assuming a 30 min dwell time and 20 min for influx and outflow, 12 2 liter exchanges can be performed overnight for an overall duration of 10 h. Finally, the third part of the curve of Fig. 2.6 is the region where the plateau is reached, and further increases in dialysate flow rates do not result in parallel increases in clearance. This region has been explored experimentally utilizing continuous flow peritoneal dialysis (CFPD) performed with double lumen peritoneal catheters [56] and theoretical mathematical models based on mass transfer-area coefficient (MTC) calculations [57]. The value of the mass transfer coefficient is a function of the product of the overall permeability of the peritoneum and the available surface area of the membrane. This parameter is based on the calculation made for each single subject of the maximal clearance theoretically achievable at infinite blood and dialysate flow rates (i.e., at a constantly maximal gradient for diffusion).

The abovementioned regions of the curve describe the relationship between dialysate flow and solute transport. Other factors such as dialysate temperature, intraperitoneal volume, and dialysate osmolality represent further factors affecting solute transport either by increasing the diffusion process or by adding some convective transport due to increased ultrafiltration rates.

The Peritoneal Dialysis Membrane The peritoneal dialysis membrane is a living structure that can be considered more a functional barrier than a precisely defined anatomical structure. Based on the flow/clearance curve described above, a question may arise: Why is the value of the MTC so low in peritoneal dialysis compared with other dialysis treatments, and is the membrane involved in such limitations?

The three-pore model has been proposed by Rippe et al. to explain the peculiar behavior of the peritoneal membrane in relation to macromolecules, micromolecules, and water transport [58]. According to this model, human peritoneum appears to behave as a membrane with a series of differently sized pores: large pores of 25 nm (macromolecule transport), small pores of 5 nm (micromolecule transport), and ultrasmall pores (water transport). The anatomical structure of these ultrasmall pores corresponds to the water channels created by a specific protein (aquaporin) acting as a carrier for water molecules.

This model locates the main resistance to transport at the level of the capillary wall, considering all other anatomical structures as a negligible site of resistance. Only recently, the interstitium has been included as an additional site of resistance. A controversial opinion is offered by the "distributed model" of Flessner et al. [59]. In this model, the main resistance to transport is apparently located in the interstitial tissue. This anatomical entity consists of a double density material, containing water and glycosaminoglycans in different proportions. The interstitial matrix seems to act as the main site of resistance to solute and water transport from the blood stream to the peritoneal cavity. The solute diffusivity in free water is greater than that in the tissue by more than one order of magnitude. Accordingly, not only the structure of the interstitium but also the thickness of the glycosaminoglycan layer may play an important role in restricting the diffusive transport of solutes. There is a certain discrepancy between the two models, and overall transport process is probably governed by a more complex and integrated series of events, each with a remarkable but not absolute importance.

The Peritoneal Microcirculation Despite several lines of evidence suggesting that peritoneal blood flow should be high enough to avoid any limitation in solute clearances and ultrafiltration, the real impact of effective blood flow on the efficiency of the peritoneal dialysis system is still controversial [60]. Experimental work has in fact suggested that peritoneal ultrafiltration and solute clearances might be blood flow limited at least in some conditions [61].

Although mesenteric blood flow averages 10% of cardiac output, peritoneal capillary blood flow seems to vary between 50 and 100 mL/min. "Effective" flow involved in peritoneal exchanges is, however, unknown and it could be much lower. Gas clearance studies have suggested that peritoneal blood flow may be as high as 68–82 mL/min [62], while other studies have suggested much lower values of effective blood flow [63]. Gas clearance studies were based on the assumption that peritoneal gas clearance is equivalent to effective blood flow, but this assumption may not necessarily represent the actual condition. In recent studies, we have obtained an indirect measure of effective blood flow of between 25 and 45 mL/min [64].

When peritoneal dialysis is carried out with short exchanges and high dialysate flows, solute clearances and ultrafiltration rate are still rather low if compared with extracorporeal HD. Some authors have hypothesized these parameters to be limited mostly by the permeability of peritoneal mesothelium or by the peritoneal membrane as a whole (vascular endothelium, interstitium, and mesothelium). As an alternative, we have proposed that peritoneal blood flow might be the major limiting factor in rapid peritoneal dialysis exchanges [63, 65, 66].

The results obtained by a study in which a fragment of human peritoneum was perfused in a closed vascular loop displayed a linear correlation between the inlet blood flow and the rate of ultrafiltration, with a stable value of the filtration fraction [61]. The linear correlation between small solute clearance and blood flow, even at these high blood flows, seems to suggest that small solute clearance in peritoneal dialysis is probably limited more by the low effective blood flow than by the low permeability of the peritoneal membrane [67]. For larger solutes such as inulin, the low diffusion coefficients of the molecule may represent the most important limitation to transport. All these observations led to the formulation of the "nearest capillary hypothesis" [68].

Considering the peritoneal microvasculature as a network of capillaries with a three-dimensional distribution and different distances from the mesothelium, the diffusion distances of solutes as well as the glucose backdiffusion distances may be different in different populations of capillaries. In this condition, the capillary situated closest to the mesothelium would experience a greater osmotic effect compared with those located further away, presenting a filtration fraction much higher compared with the others. The final effect would be represented by an average value of clearance and ultrafiltration to which proximal and distant capillaries are differently contributing. Clearance and ultrafiltration could be limited by low blood flow at least in the capillaries closest to the peritoneal mesothelium. While in distant capillaries blood flow could be enough to avoid significant limitations, the effective blood flow in the capillaries closest to mesothelium might be too low. The vascular reserve, represented by the most distant capillaries, would only participate partially in the peritoneal exchanges because of the greater distance to the mesothelium and the interference of the interstitial surrounding tissue. In such a condition, the central role of the interstitium becomes evident as well as its hydration state.

Relationship Between Clearance and Mass Removal Rate Among Various Renal Replacement Therapies

Quantification of solute removal by RRT is complicated by the confusion relating to the relationship between clearance and mass removal for different therapies. Exploring this relationship for the renal handling of urea at differing levels of native kidney function is an instructive first step. By definition [69], solute clearance (K) is the ratio of mass removal rate (N) to blood solute concentration (C_B):

$$K = N / C_B \tag{2.8}$$

From this relatively simple expression, it is clear that a defined relationship between clear-

ance and mass removal rate is not necessarily expected to exist. The assumption of a steady-state condition in this situation implies that overall removal of a solute is exactly balanced by its generation to produce a constant blood concentration. Therefore, for two patients with widely different levels of native kidney function but the same rate of urea generation (i.e., dietary protein intake), steady state is characterized by equivalent mass removal rates but significantly different urea clearance and BUN values.

The situation is more complicated in renal failure patients treated with various forms of RRT. As discussed by Henderson et al. [70], the mass removal rate of small solutes like urea is very high during the early stage of an intermittent HD treatment due to a favorable transmembrane concentration gradient for diffusion at this time. However, as this gradient dissipates, mass removal rate declines despite a constant dialyzer urea clearance (assuming dialyzer function is preserved during the treatment) (Fig. 2.7a). A different time-dependent relationship between instantaneous clearance and mass removal rate is observed during a typical CAPD exchange. As also described by Henderson et al. (Fig. 2.7b), instantaneous clearance progressively falls during the course of an exchange concomitant with a decreasing transmembrane concentration gradient. Therefore, both mass removal rate and clearance, derived by measuring solute mass in the effluent dialysate collected over

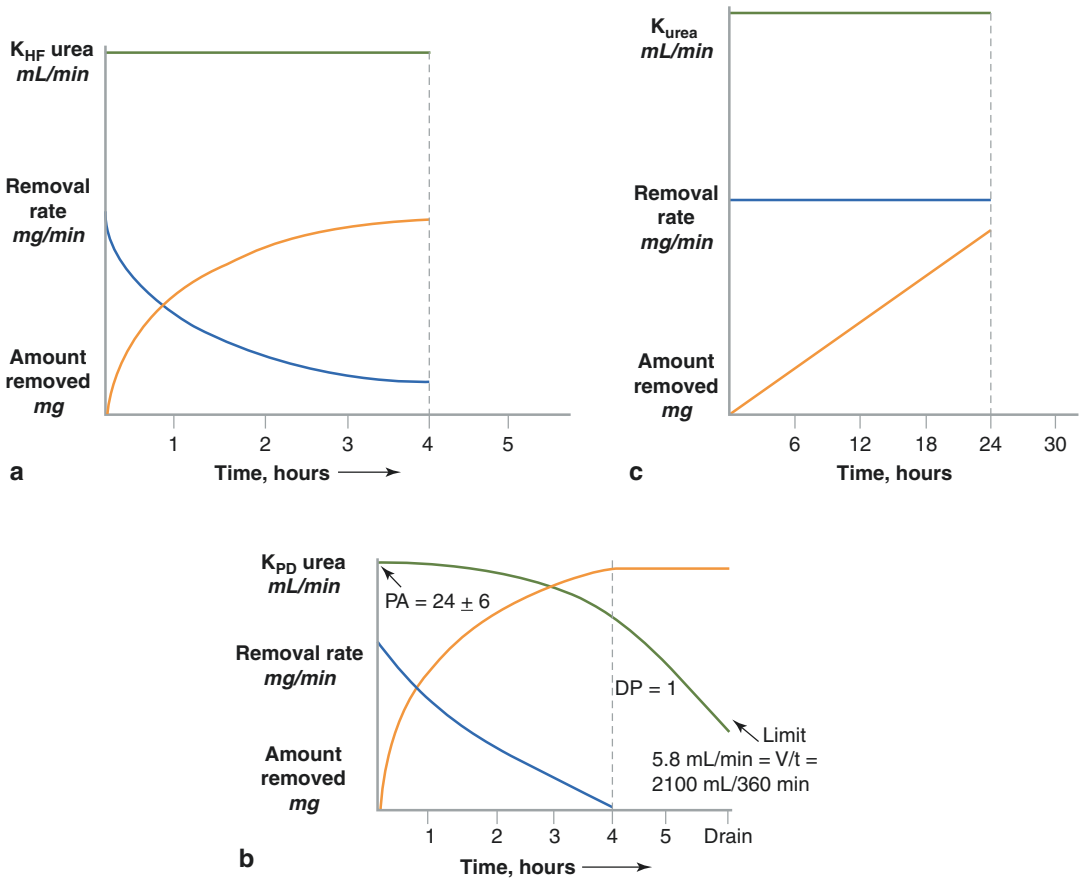

Fig. 2.7 Relationship between clearance and mass removal rate for intermittent hemodialysis (**a**), peritoneal dialysis (**b**), and continuous renal replacement therapy (**c**). (Modified from Clark and Henderson (2001) [71])

an entire exchange, are actually time-averaged parameters. Finally, continuous RRT (CRRT) used in AKI provides additional proof that the relationship between clearance and mass removal rate is therapy specific. In Fig. 2.7c, this relationship for CRRT operated at steady state with respect to BUN (in a patient with a constant protein catabolic rate) is shown [71]. In this situation, as long as urea clearance by the hemofilter is constant, mass removal rate is also constant such that the two parallel one another, and cumulative removal is related to time in a linear manner.

Clearance as a Dialyzer Performance Parameter

Whole-Blood Clearance

For a hemodialyzer, mass removal rate is simply the difference between the rate of solute mass (i.e., product of flow rate and concentration) presented to the dialyzer in the arterial bloodline and the rate of solute mass leaving the dialyzer in the venous blood line. This mass balance applied to the dialyzer results in the classical (i.e., arteriovenous) whole-blood dialyzer clearance equation [72]:

$$K_B = \left[\left(Q_{Bi} * C_{Bi}\right) - \left(Q_{Bo} * C_{Bo}\right)\right] / C_{Bi} + Q_F * \left(C_{Bo} / C_{Bi}\right) \tag{2.9}$$

In this equation, K_B is whole-blood clearance, Q_B is blood flow rate, C_B is whole-blood solute concentration, and Q_F is net ultrafiltration rate. [The subscripts "i" and "o" refer to the inlet (arterial) and outlet (venous) blood lines.]

It is important to note that diffusive, convective, and possibly adsorptive solute removal occur simultaneously in HD. For a non-adsorbing solute like urea, diffusion and convection interact in such a manner that total solute removal is significantly less than what is expected if the individual components are simply added together. This phenomenon is explained in the following way. Diffusive removal results in a decrease in solute concentration in the blood compartment along the axial length (i.e., from blood inlet to blood outlet) of the hemodialyzer. As convective solute removal is directly proportional to the blood compartment concentration, convective solute removal also decreases as a function of this axial concentration gradient. On the other hand, hemoconcentration resulting from ultrafiltration of plasma water causes a progressive increase in plasma protein concentration and hematocrit along the axial length of the dialyzer. This hemoconcentration and resultant hyperviscosity causes an increase in diffusive mass transfer resistance and a decrease in solute transport by this mechanism. The effect of this interaction on overall solute removal has been analyzed rigorously by numerous investigators. The most useful quantification has been developed by Jaffrin [73]:

$$K_T = K_D + Q_F * T_r \tag{2.10}$$

In this equation, K_T is total solute clearance, K_D is diffusive clearance under conditions of no net ultrafiltration, and the final term is the convective component of clearance. The latter term is a function of the ultrafiltration rate (Q_F) and an experimentally derived transmittance coefficient (T_r), such that:

$$T_r = S\left(1 - K_D / Q_B\right) \tag{2.11}$$

where S is solute sieving coefficient. Thus, T_r for a particular solute is dependent on the efficiency of diffusive removal. At very low values of K_D/Q_B, diffusion has a very small impact on blood compartment concentrations, and the convective component of clearance closely approximates the quantity S^*Q_F. However, with increasing efficiency of diffusive removal (i.e., increasing K_D/Q_B), blood compartment concentrations are significantly influenced. The result is

a decrease in T_r and, consequently, in the convective contribution to total clearance.

Blood Water and Plasma Clearance

An implicit assumption in the determination of whole-blood clearance is that the volume from which the solute is cleared is the actual volume of blood transiting through the dialyzer at a certain time. This assumption is incorrect for two reasons. First, in both the erythron and plasma components of blood, a certain volume is comprised of solids (proteins or lipids) rather than water. Second, for solutes like creatinine and phosphate which are distributed in both the erythron and plasma water, slow mass transfer from the intracellular space to the plasma space (relative to mass transfer across the dialyzer) results in relative sequestration (compartmentalization) in the former compartment [74–76]. This reduces the *effective* volume of distribution from which these solutes can be cleared *in the dialyzer*. As such, whole-blood dialyzer clearances derived by using plasma water concentrations in conjunction with blood flow rates, a common practice in dialyzer evaluations, result in a significant overestimation of actual solute removal. The more appropriate approach is to employ blood water clearances, which account for the above hematocrit-dependent effects on effective intradialyzer solute distribution volume [77]:

$$Q_{BW} = 0.93 * Q_B \left[1 - \mathrm{Hct} + K\left(1 - e^{-\alpha t}\right)\mathrm{Hct} \right] \tag{2.12}$$

where Q_{BW} is blood water flow rate. In this equation, for a given solute, K is the RBC water/plasma water partition coefficient for a given solute, α is the transcellular rate constant (units: time^{-1}), and t is the characteristic dialyzer residence time. Estimates for these parameters have been provided by numerous prior studies and have been summarized by Shinaberger et al. [78]. (The factor 0.93 in Eq. (2.12) corrects for the volume of plasma occupied by plasma proteins and lipids.) Finally, K_{BW} can be calculated by substituting Q_{BW} for Q_B in Eq. (2.9).

Although the distribution volume of many uremic solutes approximates total body water, it is much more limited for other toxins, particularly those of larger MW. For example, the distribution space of β2M and many other LMW proteins is the extracellular volume. Consequently, when using Eq. (2.2) to determine β2M clearance, plasma flow rates (inlet and outlet) should replace blood flow rates in the first term of the right-hand side of the equation.

The distinction between whole blood, blood water, and plasma clearances is very important when interpreting clinical data. However, clearances provided by dialyzer manufacturers are typically in vitro data generated from experiments in which the blood compartment fluid is an aqueous solution. Although these data provide useful information to the clinician, they overestimate actual dialyzer performance that can be achieved clinically (under the same conditions). This overestimation is related to the inability of aqueous-based experiments to capture the effects of red blood cells (see above) and plasma proteins (see below) on solute mass transfer.

Dialysate-Side Clearance

As indicated in Eq. (2.8), solute clearance is the ratio of mass removal rate to blood concentration. Although blood-side measurements are typically used to determine solute mass removal rate, clearance can also be estimated from dialysate-side measurements:

$$K_D = Q_{Do} * C_{Do} / C_{Bi} \tag{2.13}$$

In this equation, dialysate-side solute clearance (K_D) is determined by measuring the rate of mass appearance in the effluent dialysate stream (Q_{Do}*C_{Do}). Dialysate-side measurements provide more accurate mass transfer information than do blood-side determinations and are generally considered the "gold standard" dialyzer evaluation technique. Relative to dialysate-side values, whole-blood clearances substantially overestimate true dialyzer performance [77]. Blood water clearances also moderately overestimate dialyzer

performance, although the agreement between these and simultaneous dialysate-side values (for non-adsorbing solutes) is usually within 5% under rigorous test conditions. The major disadvantage of dialysate-based clearance techniques is the need to assay solute concentrations at very low concentrations. For some solutes (e.g., phosphate), these dilute concentrations may be difficult to assay with standard automated chemistry devices.

Whole-Body Clearance

The discussion to this point has focused on clearance of a solute by the dialyzer but has not focused on the effects of solute compartmentalization on effective dialytic removal. As discussed above, one compartment in which solute sequestration occurs is the red blood cell water. Compartmentalization may also occur during HD within other organ systems or anatomical spaces. During HD, direct removal of a particular solute can only occur from that portion of its volume of distribution which actually perfuses the dialyzer, and sequestration of solute occurs in the remaining volume of distribution. Solute compartmentalization involves an interplay between dialyzer solute clearance and patient/solute parameters, such as compartment volumes and intercompartment mass transfer resistances [79]. Even if solute removal by the dialyzer is relatively efficient, overall (effective) solute removal may be limited by slow intercompartment mass transfer within the body.

To account for these effects of "intracorporeal" solute compartmentalization on overall solute removal, many clinicians prefer to use whole-body rather than dialyzer clearance, as the former is felt to be a better measure of overall treatment efficacy [80]. Whole-body clearance methodologies employ blood samples obtained before and after the HD treatment. An example of a widely used whole-body clearance approach is the second-generation Daugirdas equation [81]. In this approach, a logarithmic relationship between delivered urea Kt/V and the extent of the intradialytic reduction in the BUN is assumed. Two issues complicate the use of these methodologies. One is the assumed distribution volume of the solute for which the clearance is being estimated and whether or not this volume is multi-compartmental. The second important consideration, incorporation of the effects of post-HD rebound, is closely tied to multi-compartment kinetics [79].

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