

Urea kinetic modeling and dialysis prescription

Dr Shirin Meshkinfar

Nephrologist

Introduction

- Dialysis is arguably a successful life-sustaining therapy. This unique, extracorporeal therapy has granted millions of people years of life after kidney failure.
- Clinicians order HD as a prescription. Like any medication prescription, the timing, frequency, and dose are all important to the efficacy of the treatment
- Nephrologists should assess the dose of HD they are prescribing by periodically measuring it. The dose of HD is the fractional clearance of urea, often referred to as the adequacy of HD.
- modeling(UKM) in determining the dose of HD in adults is an attempt to better understand complex processes

Why Model Urea?

the attributes of an ideal marker for monitoring HD adequacy would likely embody the following characteristics:

- (1) it would increase in kidney failure
- (2) it would correlate with clinical signs and symptoms of the disease
- (3) it would be removable by dialysis
- (4) it would be easy and reproducibly measurable
- (5) its degree of removal would be associated with important clinical outcomes

The Kinetics of Urea

- Understanding how the concentration of urea changes over time in the context of urea generation and dialysis removal is the value of UKM
- The urea concentration in serum, most commonly assessed as BUN, is the balance of urea production from protein breakdown and the removal of urea.
- We can judge about adequacy of dialysis to some extent but not completely

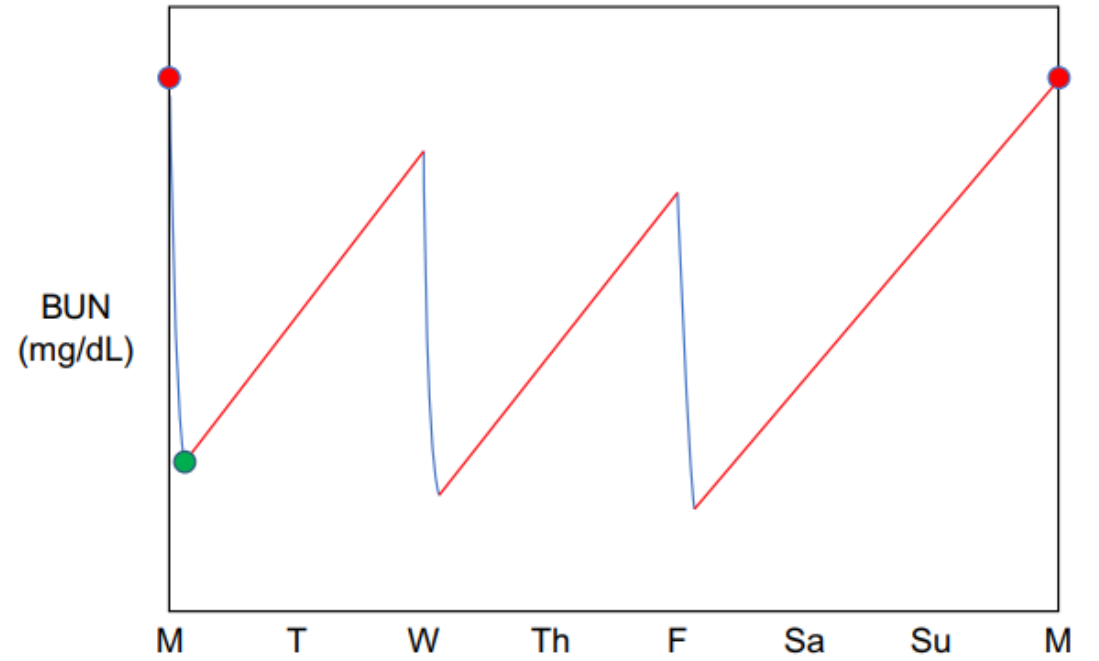
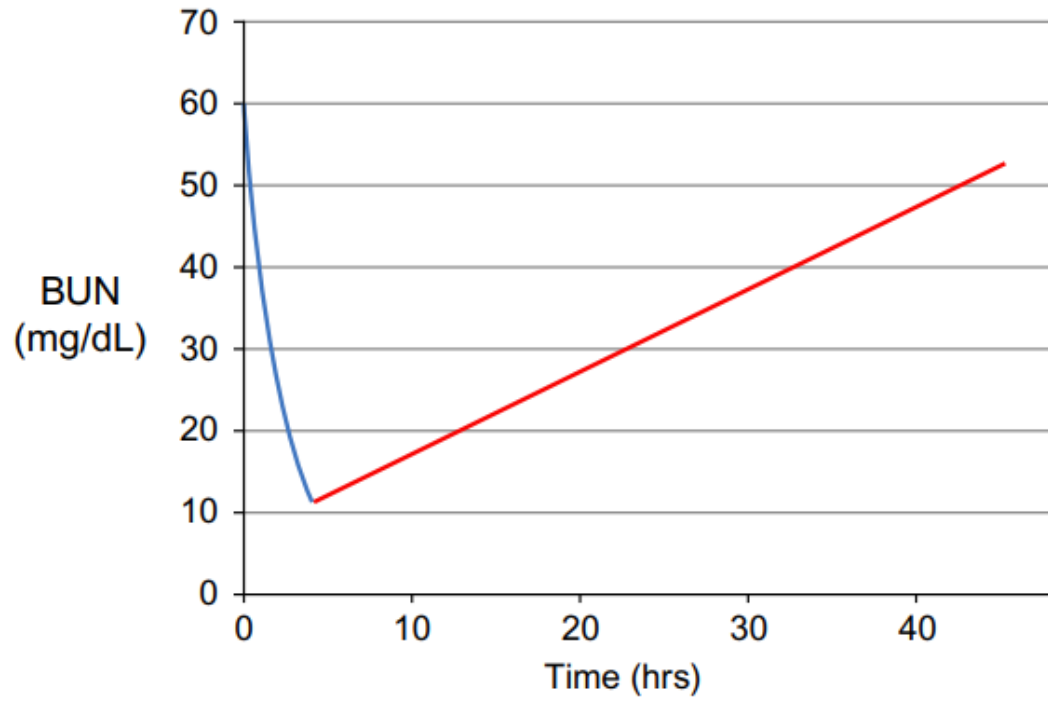
Balance Between Urea Production and Removal

- In patients with kidney failure on HD, serum urea concentration is constantly changing since its removal by HD is an intermittent process.
- Urea generation rate (G), expressed in units of mass per unit time (g/day or mg/min), for the purpose of UKM, is assumed to be constant both during and between dialysis treatments.
- Removal of urea (K) is the sum of dialyzer and native kidney clearances (KD and KR , respectively).
- concentration of urea (C) is a function of its generation rate within the body (G), the body water in which urea is distributed (V), and the clearance of urea by KD and KR

$$d(V \times C)/dt = G - K \times C$$

- Urea *generation* (G), predominantly by the liver, is a zero order kinetic process, meaning that its rate of production is not affected by the surrounding concentration.
- Urea *removal* by dialysis and native kidneys are first-order elimination processes, the urea removal rate is dependent on its concentration.
- The rate of urea elimination declines over time for both diffusive and convective clearances since the concentration of the urea in the plasma declines.
- urea concentration in the patient during HD decreases in a logarithmic fashion, and removal becomes less “efficient” over time.

typical removal and gain of urea.



a typical thrice-weekly HD profile for BUN

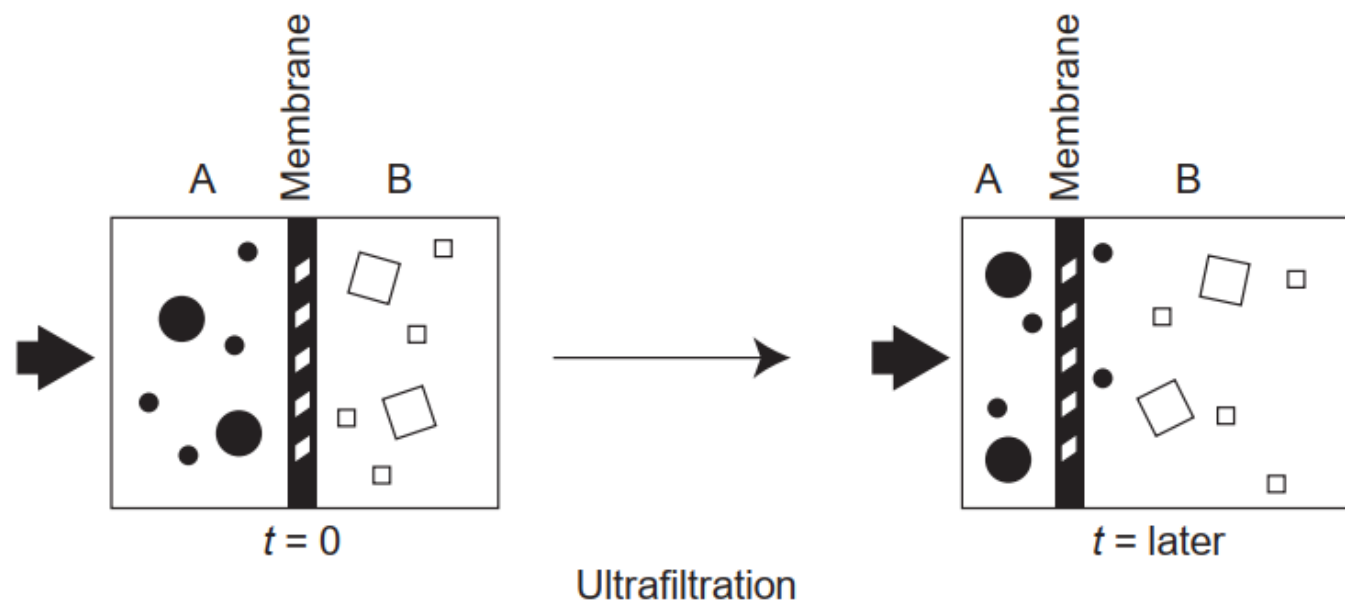
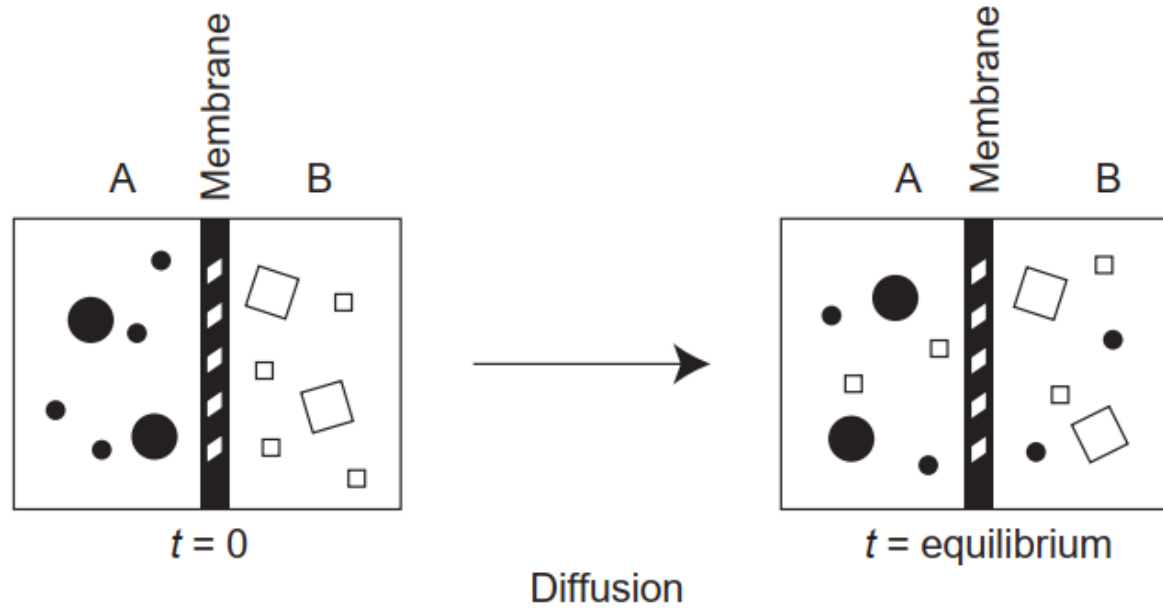
MECHANISMS OF SOLUTE TRANSPORT

Solutes that can pass through the membrane pores are transported by two different mechanisms:
Diffusion and ultrafiltration (convection)

A. Diffusion: the movement of solutes by diffusion is the result of random molecular motion. The Larger the molecular weight of a solute, the slower will be its rate of transport across a semipermeable Membrane. Small molecules their rate of diffusive transport through the membrane will be high.

B. Ultrafiltration: (convective transport) Water molecules are extremely small and can pass through All semipermeable membranes. ultrafiltration occurs when water driven by either a hydrostatic or an Osmotic force is pushed through the membrane .Those solutes that can pass easily through The membrane pores are swept along with the water

- Hydrostatic ultrafiltration
- Osmotic ultrafiltration



- During hemodialysis (HD), solutes and water are removed through a semipermeable membrane using different separation mechanisms (diffusion, convection, adsorption, and ultrafiltration)
- The traditional classification scheme for dialysis membranes has been based broadly on composition and water permeability.
- advances in biomaterials and improved fiber production (spinning) technology have led to consideration of several other parameters for membrane characterization, especially new permeability indices
- dialysis membrane is the most important determinant of HD performance (i.e., solute clearance), the dialyzer in which it is housed is the device that is actually prescribed by the clinician for treatment.

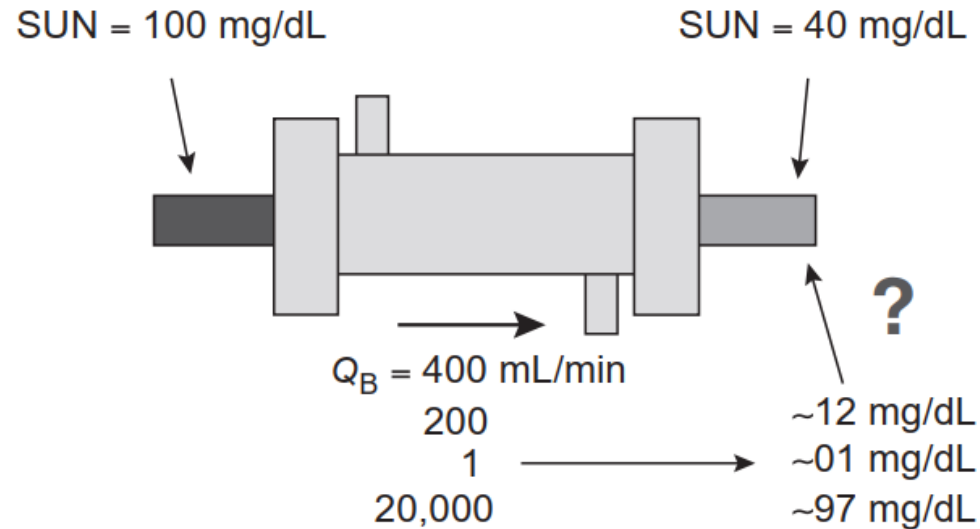
Extraction ratio

- The extraction ratio is the percentage reduction of urea (or any other solute) across the dialyzer.
- The extraction ratio is affected by the rate of blood flow through the dialyzer

Q_B (mL/min)	Outlet SUN (mg/dL)	Extraction Ratio (ER, %)	K_D (ER \times Q_B)
50	1	99	50
200	12	88	176
400	40	60	240
500	48	52	260
20,000	97	3	600

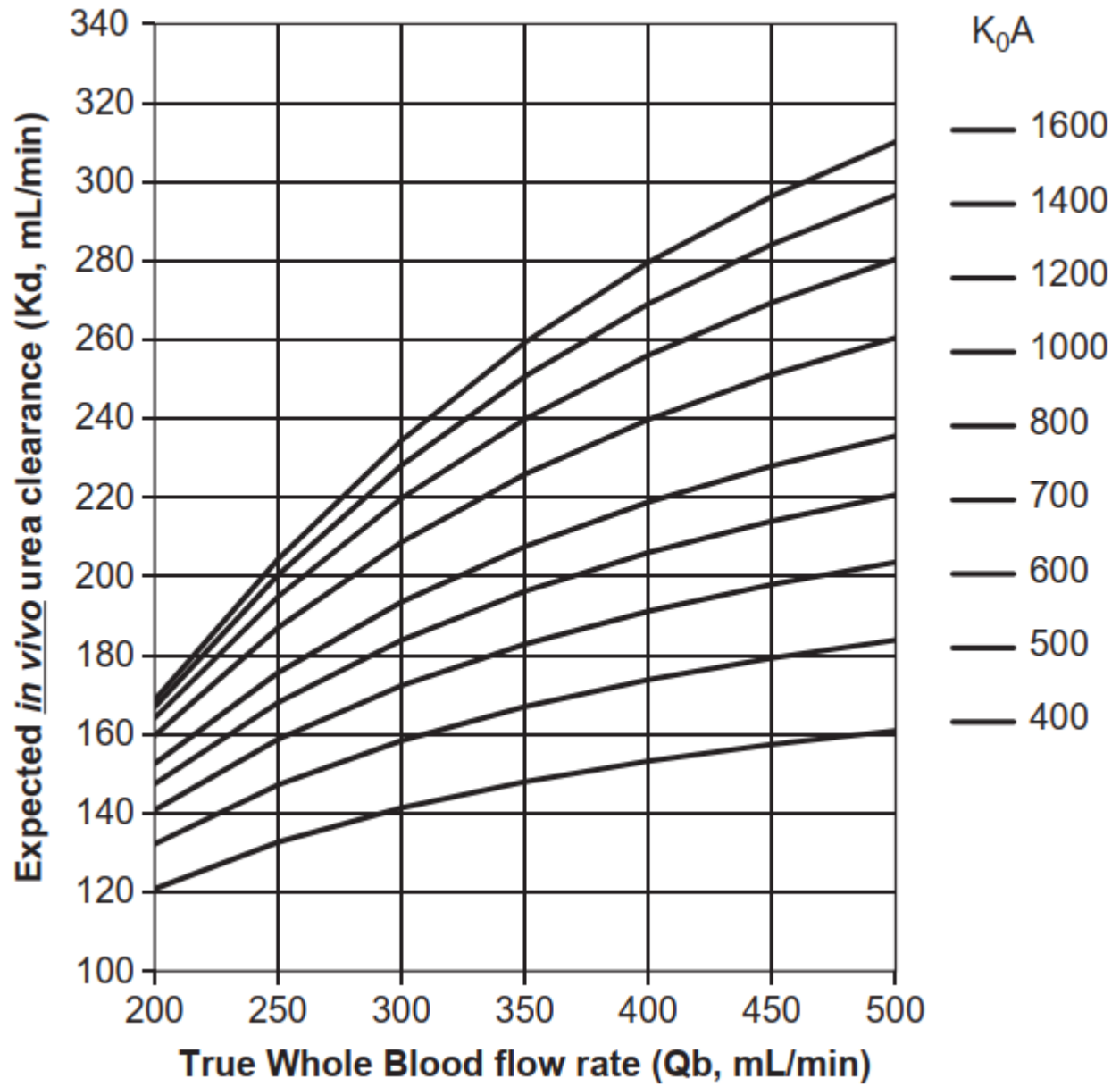
What is the effect of Q_B on ER?

The higher the Q_B , the lower the ER
 The lower the Q_B , the higher the ER



The K_0A , mass transfer area coefficient

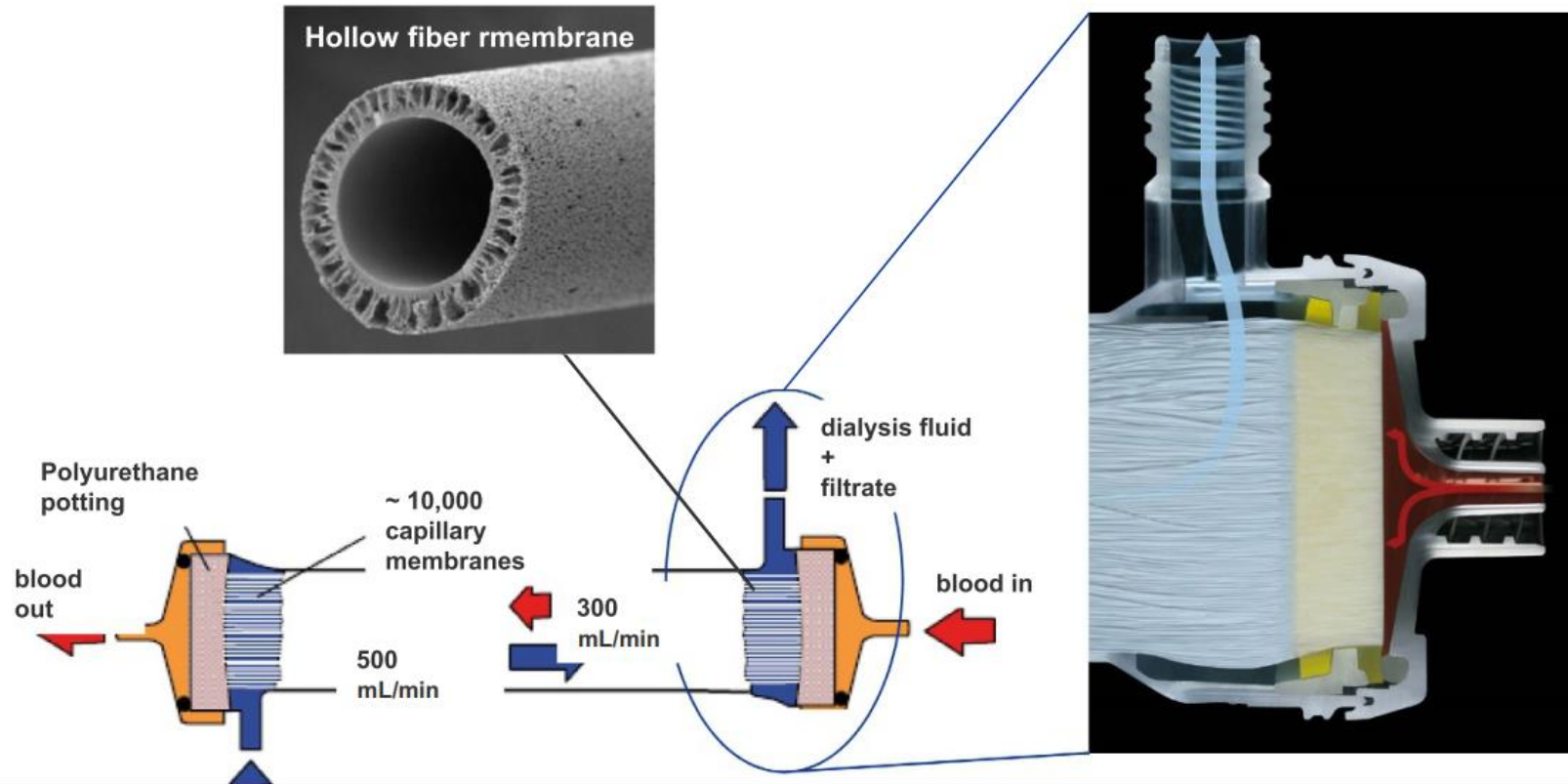
- removal efficiency falls at higher blood flow rates, and so the clearance does not increase with Q_B in a 1:1 ratio. Ultimately, at very high blood flow rate, the clearance will plateau
- The theoretical maximum clearance of a dialyzer (for a given solute) at infinite blood and dialysate flow rates is called the K_0A and has units of mL/min
- The K_0A also has a physical aspect. It is the multiple of two quantities: k_0 , the permeability coefficient of the dialyzer membrane for a given solute, and A , the total effective surface area of the membrane in the dialyzer



Hollow Fiber Dialyzers

Fundamental Considerations

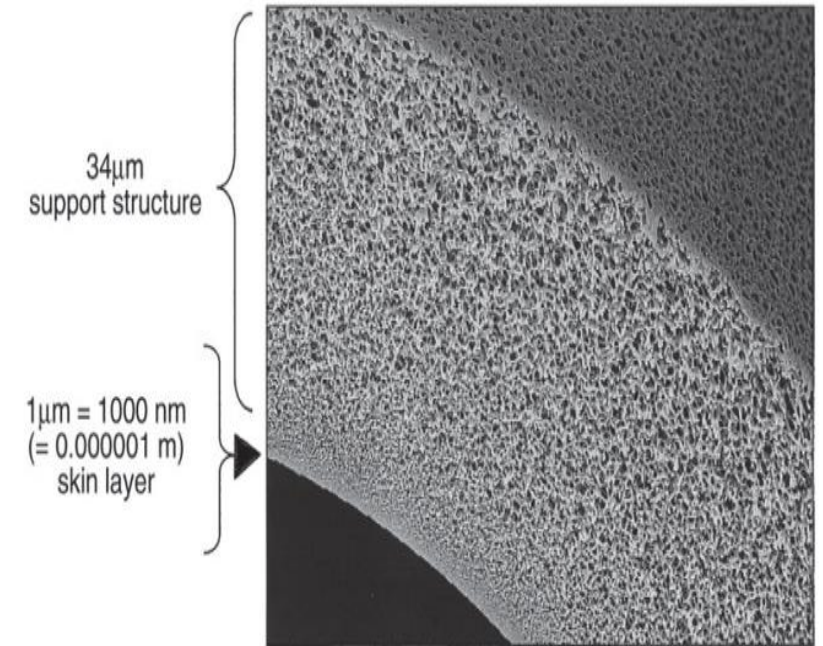
- dialysis membranes have been categorized traditionally into cellulosic and synthetic groups
- While unmodified cellulosic membranes were used extensively in the past, their utilization has dropped precipitously over the past decades to the current point of effective absence from the market
- The traditional parameter for characterization of dialysis membrane biocompatibility has been complement activation, and one of the original driving forces for the introduction of synthetic membranes was attenuation of this phenomenon (relative to unsubstituted cellulosic membranes).



Hollow Fiber Membrane Characteristics

Influencing Dialyzer Performance

- From a structural perspective, the wall thickness values for contemporary synthetic membranes generally range from 20 to 50 μm
- the majority of synthetic membranes used for contemporary HD have an asymmetric structure :a thin inner “skin” layer (approximately 1 μm or less) at the membrane–blood interface serves as the primary size-discriminating element with respect to solute removal.
- The remaining wall thickness (“stroma”) acts as a support structure that also provides substantial surface area for molecules that are removed by adsorption. As opposed to the compact nature of the skin layer, the structure of this component of the membrane is relatively open



Ultrafiltration coefficient (*KUF*).

- The permeability of dialyzer membranes to water, though high, can vary considerably and is a function of membrane thickness and pore size.
- The permeability of a membrane to water is indicated by its ultrafiltration coefficient, ***KUF***
- ***KUF*** is defined as the number of milliliters of fluid per hour that will be transferred across the membrane per mm Hg pressure gradient across the membrane.

- The clinical parameter used to quantify water permeability, K_{uf} (mL/h/mm Hg), is derived from the relationship between ultrafiltration rate (Q_f) and transmembrane pressure (TMP)
- The rate of ultrafiltrate flow through membrane pores is roughly proportional to the fourth power of the mean pore radius (i.e., r^4) of the membrane at constant TMP.
- the membrane parameter having the most significant influence on water flux is the average pore size. While the water permeability of a dialyzer is a specific property characterizing a “clean” (i.e., unfouled) membrane, its effective value is dynamically influenced by protein/membrane interactions during the course of a typical treatment

Diffusive Solute Transport During Hemodialysis

- Diffusive mass transfer in a dialyzer is typically expressed in terms of the overall resistance to mass transfer (R_0) and the overall mass transfer coefficient (K_0)

$$R_0 = R_B + R_M + R_D$$

R_B , R_M , and R_D are resistances contributed by the blood compartment, membrane, and dialysate compartment

- While blood compartment resistance typically is controlling for small solutes (irrespective of dialyzer type), membrane resistance becomes most important at a certain molecular weight

- Blood flow rate and hollow-fiber diameter (diffusion path length) are the two most important determinants of resistance to small solute mass transfer in the blood compartment
- KoA is a function of blood flow rate, dialysate flow rate, and dialyzer clearance that is measured under the condition of zero net ultrafiltration
- The requirement of zero net ultrafiltration implies that KoA is a purely diffusive parameter, and is valid for all solute-membrane combinations with low-flux dialyzers
- a zero net ultrafiltration condition is not equivalent to the absence of fluid fluxes across a high flux dialyzer membrane and a condition of “pure diffusion” is not readily attainable with this type of device

- Small solute KoA values are minimally influenced under the condition of zero net ultrafiltration and remain valid solute removal parameters for high-flux dialyzers when measured in this context.
- diffusive KoA values for larger solutes (e.g., β 2-microglobulin: β 2M) cannot be estimated reliably under these conditions, as the convective clearance associated with fluid fluxes (“internal filtration”) contributes significantly to total clearance
- KoA values for molecules other than urea and creatinine have little clinical meaning.

Removal of Large Molecular Weight Uremic Toxins

Convective Transport

- As effective solute molecular weight increases, diffusive transport becomes increasingly limited. This limitation can be overcome by the introduction of convective transport, which relies on the mechanism of solvent drag. rate of convective solute removal is proportional to ultrafiltration rate
- The parameter classically used to define the convective membrane transport properties for a specific solute is the sieving coefficient :

$$SC = C_f/C_p$$

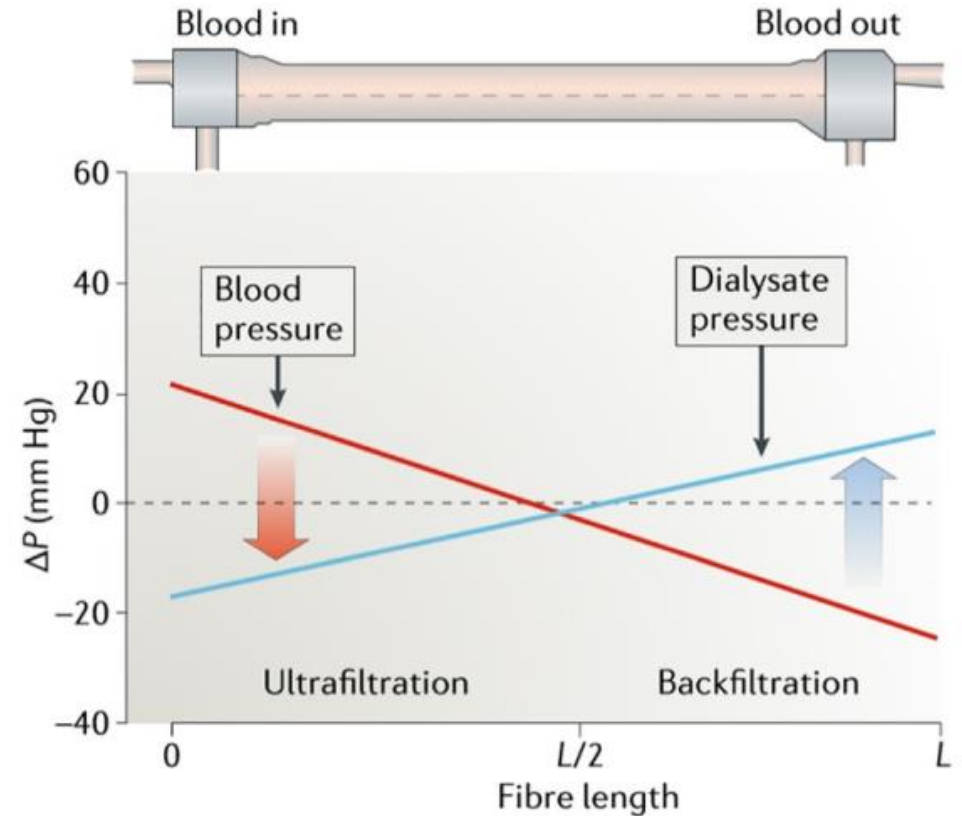
(C_f) is solute concentration in the filtrate, (C_p) is the solute concentration under conditions of “pure” ultrafiltration (i.e., no dialysate flow)

- The observed (measured) sieving coefficient values are influenced by interactions that occur between the membrane and blood elements during dialysis removal of specific solutes, the influence of secondary membrane formation is directly proportional to solute molecular weight.

Other Mechanisms Influencing Large Solute Removal

- current membranes, even those that have been considered traditionally to be highly permeable, provide limited clearance of compounds larger than 10 kDa
- Even though these membranes have relatively large mean pore sizes, they still offer substantial mass transfer resistance to the diffusive removal of large solutes.
- fouling has a significant impact on convective solute clearances, especially for molecules larger than 10 kDa
- These constraints are particularly relevant under conditions involving high ultrafiltration rates, which promote secondary membrane formation by more effectively delivering plasma proteins to the membrane surface through convection (versus diffusion)

The pressure drop is sufficiently large that, at some point along the length of the dialyzer, the blood compartment pressure becomes less than the dialysate compartment pressure under normal operating conditions. Thus, especially considering the oncotic effects in the blood compartment, there is a point at which ultrafiltrate begins to be driven from the dialysate to the blood as opposed to the “standard” (blood to dialysate) direction in the more proximal part of the dialyzer



- The adsorptive removal of a low molecular weight protein (e.g., β 2 microglobulin) normally eliminated by the kidney is considered distinct
- adsorption of such compounds is limited to the nominal (blood-contacting) surface of the hollow fiber because they generally do not have access to the much larger surface area of the internal pore structure
- albumin is the exception to this general rule. On the other hand, adsorptive removal of smaller proteins that gain access to the large surface area of the internal pore structure can be quantitatively important, contributing to clinically relevant decreases in plasma concentrations during treatment.

Membrane efficiency versus flux

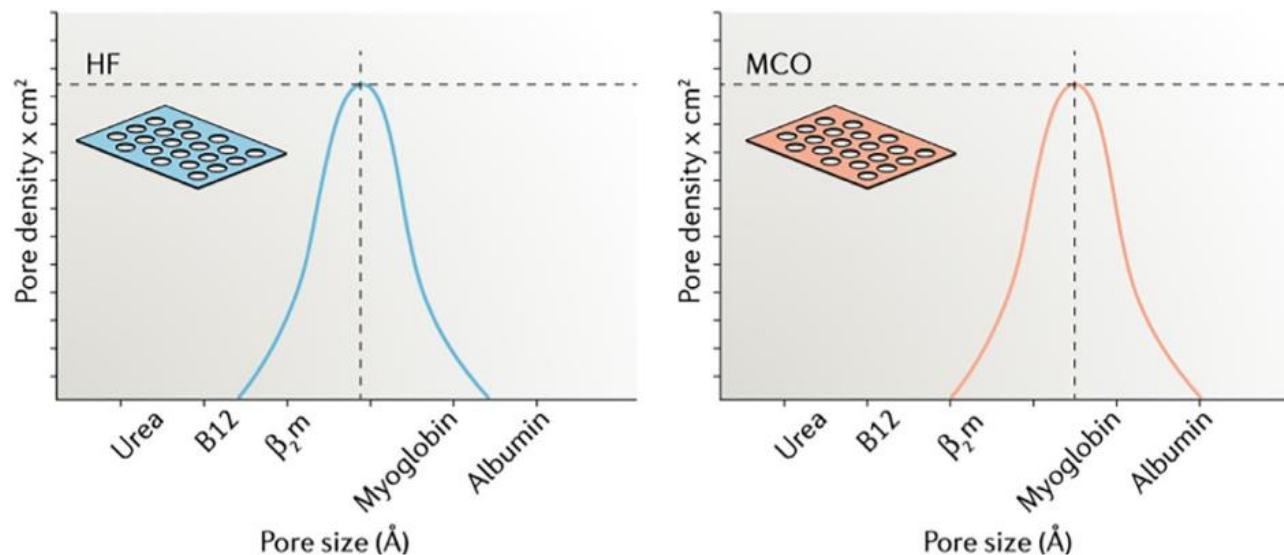
- When we speak of dialyzer efficiency, we refer primarily to the ability of a dialyzer to remove small solutes.
- The dialyzer efficiency is best represented by the K_0A for urea
- The flux of a dialyzer refers to its ability to remove very large molecules such as β_2 -microglobulin.
- There is no single measure in common use to specify the flux of a dialyzer, though water permeability (**KUF**) can be used

New Approaches for Classifying Dialysis Membranes and Dialyzers

- Larger uremic toxins are generally considered to be clinically important, and more effective dialytic removal strategies may improve patient outcomes
- the most commonly used parameter for classification purposes remains K_{uf} , with a value of 12 mL/h/mm Hg differentiating low-permeability and high-permeability dialyzers according to the U.S. Food and Drug Administration
- a revised definition used for the HEMO Trial represented an improvement. In this definition, the two high-flux criteria were K_{uf} greater than 14 mL/h/mm Hg and first-use β_2 macroglobulin clearance of greater than 20 mL/min
- a first-use β_2 microglobulin clearance of less than 10 mL/min defined a low-flux dialyzer
- the European Dialysis (EUDIAL) Group defines a high-flux dialyzer as one having an ultrafiltration coefficient greater than 20 mL/h/mm Hg/m² and a β_2 microglobulin sieving coefficient greater than 0.6

- Investigators most recently have proposed classification schemes focused even further on solute permeability properties.
- Ward defined high-flux and “protein-leaking” dialyzers based on a combination of water permeability, β_2 macroglobulin removal parameters (sieving coefficient/clearance), and albumin parameters (sieving coefficient/amount removed)
- The high-flux class was defined by a water permeability of 20–40 mL/h/mm Hg/m², β_2 microglobulin sieving coefficient of 0.7–0.8, and albumin loss (based on a 4-hour HD treatment) of less than 0.5 gm

- A higher permeability dialyzer class incorporating medium cutoff (MCO) membranes has been proposed more recently.
- The goal of this dialyzer class is to enhance large solute removal (relative to standard high-flux dialyzers) by intentionally augmenting the extent of internal filtration through a combination of increased membrane permeability (pore size) along with higher axial blood compartment resistance (decreased hollow fiber inner diameter).
- Although standard high-flux membranes made possible the development of convective therapies, MCO dialyzers membranes represent the basis for a new diffusion-based therapy called expanded HD



Philosophy of Dialysis Adequacy

- the most fundamental prescriptive question is *how much dialysis is enough? What are the direct objectives of dialysis?* The question itself may be too simplistic in
- that it does not account for the need to potentially tradeoff among objectives (e.g., maximizing survival versus creating the least burden on quality of life).
- *Is there a threshold of “enough,”* ? the right question may not be “how much is enough?” but rather “when is enough enough?.”
- Perhaps because these issues are so complex and interdependent, research and practice in dialysis have found a need to invoke simplifying paradigms and ask more directive, research-ready questions with empiric answers.

- in determining how much dialysis is enough, one must define the means by which dialysis can be quantified.
- The National Cooperative Dialysis Study was the first rigorous attempt to do so:
 - ✓ how does one provide dialysis to patients in order that they not be uremic?
 - ✓ Investigators considered two metrics of dialysis dose: time-average blood urea concentration (50 vs 100 mg/dL) and time on dialysis (2.5–3.5 vs 4.5–5 hours) and randomized patients accordingly using a 2 × 2 factorial design.
- Upon trial termination, time-average blood urea was clearly associated with patient outcomes, whereas time on dialysis did not bear statistical significance.

Kt/V

- Kt/V is the mathematical relationship between the rate of urea removal (K) times treatment duration (t) divided by the volume of distribution for urea (V).

$$\text{Daugirdas II } \frac{Kt}{V} = -\ln(R - (0.008 \times t)) + (4 - (3.5 \times R)) \times \frac{UF}{\text{PostWt}}$$

R is [post BUN]/[pre BUN], t is duration of HD in hours, UF is volume of ultrafiltration in liters, and Post Wt is patient weight after HD in kilograms.

- The first term in the equation (quantitatively the most important) describes the amount of urea that is removed from the start to the end of a dialysis treatment; this is an alternative mathematical formulation of the urea reduction ratio (URR)
- The second term in the equation corrects for urea generation during the dialysis treatment itself
- The third term in the equation accounts for urea that is removed convectively through ultrafiltration

Urea Reduction Ratio

URR is a measure of the proportionate reduction in BUN over the course of dialysis. It is calculated as:

$$\text{URR} = 100\% \times \left(\frac{\text{predialysis BUN} - \text{postdialysis BUN}}{\text{predialysis BUN}} \right)$$

It is an alternative expression of the R term in the Daugirdas equation for spKt/V

Discrepancies between URR and spKt/V derive from three primary sources:

- URR is not directly indexed to body
- URR does not directly account for urea generation during dialysis,
- URR does not account directly for convective urea losses.

Minimal Input Data Required for 2-BUN, Variable Volume Urea Kinetic Modeling

Pre- and post-HD BUN

$K_{\text{O}}\text{A}$ (mass area transfer coefficient for urea) of dialyzer

Blood flow rate

Dialysate flow rate

Duration of dialysis

Pre-HD weight

Post-HD weight

Frequency of HD per week

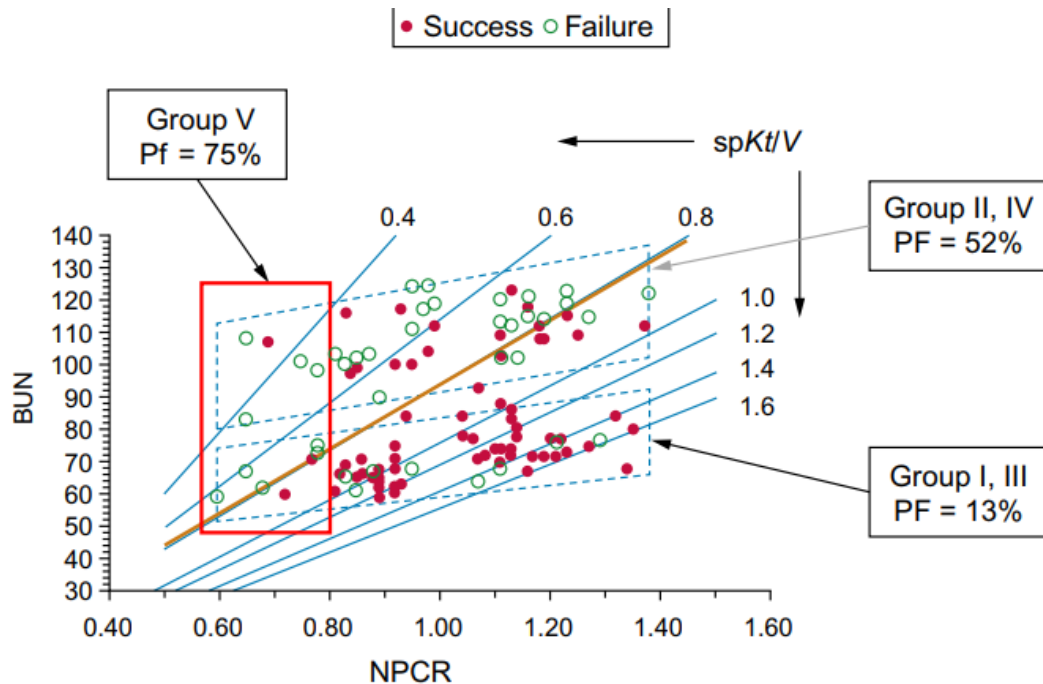
Schedule of HD (Monday, Wednesday, and Friday,
for example)

Day of the week of blood tests (Monday, for example)

BUN, Blood urea nitrogen; *HD*, hemodialysis.

Studies Assessing Dialysis Adequacy

the National Cooperative Dialysis Study (NCDS) was the first U.S. National Institutes of Health (NIH)– sponsored study looking at outcomes based on dose of dialysis as prescribed and monitored by UKM



Study Groups of the National Cooperative Dialysis Study (NCDS) by HD Duration and Pre-HD BUN

Group	Duration on Dialysis (hours:minutes)	Predialysis BUN
I (long treatment, high dose)	4:29	71.2
II (long treatment, low dose)	4:31	104.9
III (short treatment, high dose)	3:19	73.1
IV (short treatment, low dose)	3:14	109.1

BUN, Blood urea nitrogen; HD, hemodialysis.

The HEMO study definitively showed:

- $\text{spKt/V} < 1.0$ an inadequate dose of dialysis and associated with poor outcomes.
- it is unclear if there is any advantage of spKt/V greater than that and there is no advantage of $\text{spKt/V} > 1.4$
- HEMO addressed the high-dose controversy left by NCDS there was any improvement in outcomes across a moderate dosage range of 1.0–1.4.
- It is confident in declaring $\text{spKt/V} < 1.0$ an inadequate dose of dialysis and associated with poor outcomes

Thresholds for spKt/V and URR

- Survival was incrementally higher at URR up to 65% and at higher spKt/V up to 1.2.
- guidelines were issued that espouse spKt/V of 1.4 and/or URR of 70% indicative of minimally adequate dialysis
- **Practice guidelines currently recommend a minimum delivered spKt/V of 1.2 over three-weekly HD treatments**
- In fact, a prescribed dose of 1.3–1.4 is advised by experts to ensure that no patient receives below the recommended dose.

Equilibrated Kt/V

- Urea is small (molecular weight 60 D) and uncharged, which are ideal characteristics for promoting passive diffusion across lipid bilayers
- Individual vascular beds are differentially perfused. Urea present in less perfused tissues has less access to the central circulation and, thereby, is less available for dialytic removal.
- there are vascular beds for which perfusion decreases during dialysis (in response to circulatory stimuli and the neuroendocrine milieu)
- $spKt/V$ and typically URR as well are calculated based on urea concentrations measured at the end of the dialysis treatment. These levels reflect well the behavior of urea in the blood at other highly perfused tissues; they do not reflect the behavior of urea in more inaccessible tissues. Thereby, $spKt/V$ and URR tend to overestimate total body urea clearance

- Equilibrated Kt/V (eKt/V) is a metric used to account for the overestimation inherent to $spKt/V$ and is derived by sampling post dialysis blood 30 minutes following dialysis as opposed to immediately at the end of treatment.

$spKt/V$	t (hr)	$spKt/V$ per hour	Rebound	eKt/V
1.2	6	0.2	0.09	1.11
1.2	3	0.4	0.17	1.03
1.2	2	0.6	0.24	0.96

- As is evident from the table, eKt/V can be significantly less than $spKt/V$, especially during short dialysis treatments.
- the European Best Practices guidelines set their minimum recommended dialysis Kt/V of 1.2 in terms of eKt/V rather than $spKt/V$

Standardized Kt/V

- Standardized Kt/V is a concept that has been introduced in an attempt to account for modalities other than thrice weekly in-center hemodialysis
- Standardized Kt/V attempts to account for these factors by considering solute removal over the course of the week rather than for individual treatments
- The most recent guidelines from the International Society for Peritoneal Dialysis acknowledge a nominal target standardized Kt/V of 1.7.

- From the timed urine collection one knows how much creatinine is being generated per minute, and if we know the plasma concentration during the collection period, we know how much plasma is being cleared to remove the amount of creatinine that is being generated to maintain steady state

This type of calculation was adapted to hemodialysis and urea removal by Casino and Lopez (1996) a urea modeling program can obtain a value for urea generation rate for any dialysis schedule, assuming steady state.

The same modeling program can then calculate the time-averaged concentration of SUN (TAC) for the week. Once g and TAC are known, an equivalent urea clearance (EKRU) can be calculated for any dialysis regimen

$$\text{EKRU} = g / \text{TAC}$$

- EKRU can be thought of as a $(K \times t)$ term, or volume of plasma cleared during the week, and this can then be normalized to V to calculate a weekly equivalent Kt/V urea.

- The most recent guidelines from the International Society for Peritoneal Dialysis acknowledge a nominal target standardized Kt/V of 1.7.
- the guidelines explicitly recognize the limitations of narrowly focusing on small molecule clearance, or indeed on any single aspect of care, and recommend instead a more holistic assessment of dialysis adequacy that focuses on:

maintaining [patients'] clinical well-being, quality of life, ability to meet life goals and at the same time minimize treatment burden.

Middle Molecule Clearance

- “middle molecules” are a group of compounds that are biologically relevant but are removed less efficiently by dialysis.
- middle molecules also encompass low-molecular-weight compounds that are inefficiently removed during dialysis due to polyvalence (which limits dialytic membrane flux), protein binding, or intracellular sequestration. The effects of certain middle molecules such as phosphate and B2-microglobulin have been extensively studied
- Emerging evidence suggests that metabolic byproducts such as p-cresol sulfate, indoxyl sulfate, methylamine, and dimethylamine may be relevant uremic solutes, but these have received comparatively less study
- it is unlikely—that all middle molecules will behave similarly to one another with respect to dialytic removal.
- At present, there is no reliable means by which to consider middle molecules into the calculus of dialysis adequacy. Additional research in this area is sorely needed.

Fluid Removal

- dialysis “adequacy” (meaning low molecular weight clearance) and fluid removal are considered in parallel.
- Trainees are typically taught that treatment time is determined by Kt/V considerations and fluid status by specification of target weight
- ultrafiltration rate portends both labile blood pressure during dialysis and frank intradialytic hypotension, which, in turn, are associated with transient interruptions in end-organ perfusion
- recent work demonstrates that low blood pressure during dialysis (e.g., <90 mm Hg; <100 mm Hg) is associated with increased risk of all-cause and cardiovascular mortality, and in fact, this relationship is not potentiated when only symptomatic episodes are considered
- transient interruptions in perfusion, often asymptomatic in nature, contribute substantively to transient myocardial stunning and white matter damage, which in turn are associated with cardiovascular events and neurocognitive deficits, respectively

- it is not surprising that more rapid ultrafiltration is associated with a greater risk of mortality, particularly cardiovascular mortality
- greater interdialytic weight gain both implies more rapid ultrafiltration and independently associates with poor prognosis.
- matched pair analysis indicates that even if patients are exactly matched on interdialytic weight gain (and body weight), those with the higher ultrafiltration rate (i.e., those with lower treatment time) have a higher adjusted risk of death
- Differences in interdialytic weight gain between smaller and larger patients are comparatively less than differences in time needed to achieve spKt/V targets; thereby, smaller patients tend to have higher ultrafiltration rates, on average, than do larger patients, whereby smaller patients consistently demonstrate poorer survival than larger patients

- ultrafiltration rate has been studied as an average rate for dialysis sessions: net fluid removal divided by total treatment time indexed to body weight
- Best available evidence suggests that risk begins to inflect when ultrafiltration rate crosses 10 mL/h/kg body weight and becomes statistically significantly elevated when in excess of 13 mL/h/kg body weight
- Unfortunately, a recently completed clinical trial has shown that ultrafiltration profiling, the technique by which the rate of ultrafiltration is varied over the course of dialysis in an attempt to better match patients' physiology, which previously had been thought to ameliorate hypotension and promote hemodynamic stability, was ineffective in this regard

- The sobering reality is that patients do not want more dialysis, whether in the form of longer or more frequent treatments. In a recent survey, fewer than one-quarter of respondents indicated a willingness to extend treatment time by 30 minutes, and fewer than one-eighth indicated that they would be willing to increase the frequency of dialysis.

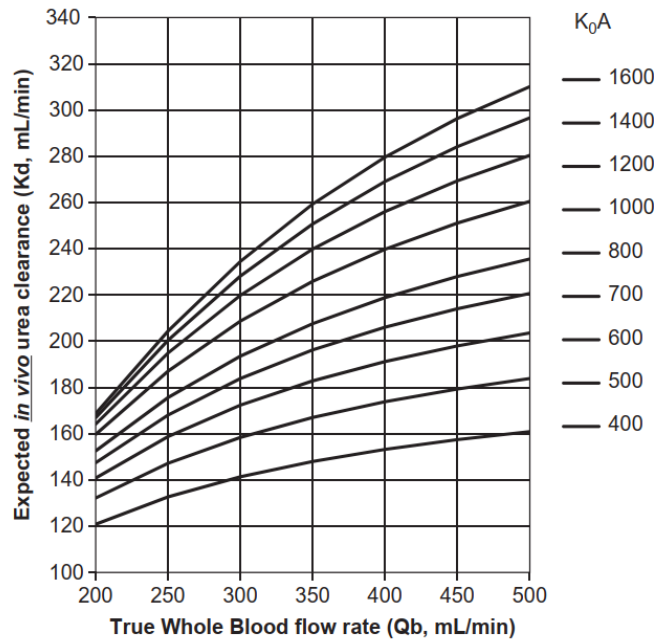
- additional patient education is needed to underscore the benefits of mitigating excessive fluid removal rates.

Conclusion

- In conclusion, urea kinetics—specifically the achievement of an spKt/V of 1.2 and/or a URR of 65%—are a necessary component of adequate dialysis.
- Emerging evidence indicates that the prescription should also include a tolerable ultrafiltration rate—optimally less than 10 mL/h/kg but certainly no more than 13 mL/h/kg.
- Available data do not inform with respect to how best to incorporate middle molecule clearance into the dialysis prescription, but the reader is advised to monitor the literature for advances in this regard.
- Finally, as in all of clinical medicine, care should be tailored to individual patients based on circumstances and preferences rather than in a cookie-cutter approach.

Pt BW: 49 kg
 Kt/v:1.2
 Time:4 h(240 min)
 QB:250
 Right filter:?

$1.2 \times 0.6 \times 49 \times 1000 / 240 = 147$
 KOA:700 , filter : pes 16 lf or ps 100 hf



نوع فیلتر	مقاومت هیدرولیک (mmHg)	فیلتراسیون				پرفورمانس				K ₀ A (mL/min)	Kt/V (min)	
		Q _b 200	Q _b 300	Q _d 200	Q _d 300	Q _b 200	Q _b 300	Q _d 200	Q _d 300			
PS 05 LF	1.2	110	110	110	110	110	110	110	110	110	110	110
PS 10 LF	1.2	110	110	110	110	110	110	110	110	110	110	110
PS 15 LF	1.2	110	110	110	110	110	110	110	110	110	110	110
PS 20 LF	1.2	110	110	110	110	110	110	110	110	110	110	110
PS 25 LF	1.2	110	110	110	110	110	110	110	110	110	110	110
PS 30 LF	1.2	110	110	110	110	110	110	110	110	110	110	110
PS 35 LF	1.2	110	110	110	110	110	110	110	110	110	110	110
PS 40 LF	1.2	110	110	110	110	110	110	110	110	110	110	110
PS 45 LF	1.2	110	110	110	110	110	110	110	110	110	110	110
PS 50 LF	1.2	110	110	110	110	110	110	110	110	110	110	110
PS 55 LF	1.2	110	110	110	110	110	110	110	110	110	110	110
PS 60 LF	1.2	110	110	110	110	110	110	110	110	110	110	110
PS 65 LF	1.2	110	110	110	110	110	110	110	110	110	110	110
PS 70 LF	1.2	110	110	110	110	110	110	110	110	110	110	110
PS 75 LF	1.2	110	110	110	110	110	110	110	110	110	110	110
PS 80 LF	1.2	110	110	110	110	110	110	110	110	110	110	110
PS 85 LF	1.2	110	110	110	110	110	110	110	110	110	110	110
PS 90 LF	1.2	110	110	110	110	110	110	110	110	110	110	110
PS 95 LF	1.2	110	110	110	110	110	110	110	110	110	110	110
PS 100 LF	1.2	110	110	110	110	110	110	110	110	110	110	110
PS 105 LF	1.2	110	110	110	110	110	110	110	110	110	110	110
PS 110 LF	1.2	110	110	110	110	110	110	110	110	110	110	110
PS 115 LF	1.2	110	110	110	110	110	110	110	110	110	110	110
PS 120 LF	1.2	110	110	110	110	110	110	110	110	110	110	110
PS 125 LF	1.2	110	110	110	110	110	110	110	110	110	110	110
PS 130 LF	1.2	110	110	110	110	110	110	110	110	110	110	110
PS 135 LF	1.2	110	110	110	110	110	110	110	110	110	110	110
PS 140 LF	1.2	110	110	110	110	110	110	110	110	110	110	110
PS 145 LF	1.2	110	110	110	110	110	110	110	110	110	110	110
PS 150 LF	1.2	110	110	110	110	110	110	110	110	110	110	110
PS 155 LF	1.2	110	110	110	110	110	110	110	110	110	110	110
PS 160 LF	1.2	110	110	110	110	110	110	110	110	110	110	110
PS 165 LF	1.2	110	110	110	110	110	110	110	110	110	110	110
PS 170 LF	1.2	110	110	110	110	110	110	110	110	110	110	110
PS 175 LF	1.2	110	110	110	110	110	110	110	110	110	110	110
PS 180 LF	1.2	110	110	110	110	110	110	110	110	110	110	110
PS 185 LF	1.2	110	110	110	110	110	110	110	110	110	110	110
PS 190 LF	1.2	110	110	110	110	110	110	110	110	110	110	110
PS 195 LF	1.2	110	110	110	110	110	110	110	110	110	110	110
PS 200 LF	1.2	110	110	110	110	110	110	110	110	110	110	110
PS 205 LF	1.2	110	110	110	110	110	110	110	110	110	110	110
PS 210 LF	1.2	110	110	110	110	110	110	110	110	110	110	110
PS 215 LF	1.2	110	110	110	110	110	110	110	110	110	110	110
PS 220 LF	1.2	110	110	110	110	110	110	110	110	110	110	110
PS 225 LF	1.2	110	110	110	110	110	110	110	110	110	110	110
PS 230 LF	1.2	110	110	110	110	110	110	110	110	110	110	110
PS 235 LF	1.2	110	110	110	110	110	110	110	110	110	110	110
PS 240 LF	1.2	110	110	110	110	110	110	110	110	110	110	110
PS 245 LF	1.2	110	110	110	110	110	110	110	110	110	110	110
PS 250 LF	1.2	110	110	110	110	110	110	110	110	110	110	110
PS 255 LF	1.2	110	110	110	110	110	110	110	110	110	110	110
PS 260 LF	1.2	110	110	110	110	110	110	110	110	110	110	110
PS 265 LF	1.2	110	110	110	110	110	110	110	110	110	110	110
PS 270 LF	1.2	110	110	110	110	110	110	110	110	110	110	110
PS 275 LF	1.2	110	110	110	110	110	110	110	110	110	110	110
PS 280 LF	1.2	110	110	110	110	110	110	110	110	110	110	110
PS 285 LF	1.2	110	110	110	110	110	110	110	110	110	110	110
PS 290 LF	1.2	110	110	110	110	110	110	110	110	110	110	110
PS 295 LF	1.2	110	110	110	110	110	110	110	110	110	110	110
PS 300 LF	1.2	110	110	110	110	110	110	110	110	110	110	110
PS 305 LF	1.2	110	110	110	110	110	110	110	110	110	110	110
PS 310 LF	1.2	110	110	110	110	110	110	110	110	110	110	110
PS 315 LF	1.2	110	110	110	110	110	110	110	110	110	110	110
PS 320 LF	1.2	110	110	110	110	110	110	110	110	110	110	110
PS 325 LF	1.2	110	110	110	110	110	110	110	110	110	110	110
PS 330 LF	1.2	110	110	110	110	110	110	110	110	110	110	110
PS 335 LF	1.2	110	110	110	110	110	110	110	110	110	110	110
PS 340 LF	1.2	110	110	110	110	110	110	110	110	110	110	110
PS 345 LF	1.2	110	110	110	110	110	110	110	110	110	110	110
PS 350 LF	1.2	110	110	110	110	110	110	110	110	110	110	110
PS 355 LF	1.2	110	110	110	110	110	110	110	110	110	110	110
PS 360 LF	1.2	110	110	110	110	110	110	110	110	110	110	110
PS 365 LF	1.2	110	110	110	110	110	110	110	110	110	110	110
PS 370 LF	1.2	110	110	110	110	110	110	110	110	110	110	110
PS 375 LF	1.2	110	110	110	110	110	110	110	110	110	110	110
PS 380 LF	1.2	110	110	110	110	110	110	110	110	110	110	110
PS 385 LF	1.2	110	110	110	110	110	110	110	110	110	110	110
PS 390 LF	1.2	110	110	110	110	110	110	110	110	110	110	110
PS 395 LF	1.2	110	110	110	110	110	110	110	110	110	110	110
PS 400 LF	1.2	110	110	110	110	110	110	110	110	110	110	110
PS 405 LF	1.2	110	110	110	110	110	110	110	110	110	110	110
PS 410 LF	1.2	110	110	110	110	110	110	110	110	110	110	110
PS 415 LF	1.2	110	110	110	110	110	110	110	110	110	110	110
PS 420 LF	1.2	110	110	110	110	110	110	110	110	110	110	110
PS 425 LF	1.2	110	110	110	110	110	110	110	110	110	110	110
PS 430 LF	1.2	110	110	110	110	110	110	110	110	110	110	110
PS 435 LF	1.2	110	110	110	110	110	110	110	110	110	110	110
PS 440 LF	1.2	110	110	110	110	110	110	110	110	110	110	110
PS 445 LF	1.2	110	110	110	110	110	110	110	110	110	110	110
PS 450 LF	1.2	110	110	110	110	110	110	110	110	110	110	110
PS 455 LF	1.2	110	110	110	110	110	110	110	110	110	110	110
PS 460 LF	1.2	110	110	110	110	1						



THANK

YOU