Dialysis Prescription and Adequacy

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Background

When dialysis was first used to treat acute renal failure in the 1940's, its overwhelming success in reversing the dreaded and commonly fatal uremic syndrome supported the concept that uremia results from a toxic effect of accumulated solutes that are normally excreted by the kidneys [38]. Equally impressive results in the 1960's when dialysis was first used to treat end-stage renal failure (ESRD), confirmed this impression [59]. Thousands of people who previously had no hope of survival have extended their lives with this modality that has come to be regarded, with the passage of time and accumulation of experience, less as a treatment and more as a preventative measure. Using this preemptive approach to prevent uremic intoxication, dialysis caregivers seek to sustain near-normal quality of life for people with ESRD. The treatment plan, which includes measuring the effect of dialysis and comparing the measurement with established standards, would be easy to monitor if the major toxins responsible for the uremic syndrome were known and could be measured. Unfortunately, despite many decades of research, no single toxin or group of toxins has been pinpointed as the cause of one or more of the symptoms and/or signs of uremia. Instead clinicians are limited to measuring serum concentrations of familiar small solutes, like urea and creatinine, that are known to depend on native renal function for elimination but have little inherent toxicity. Because they accumulate rapidly to relatively high levels and dialyze easily, these familiar compounds are better measures of the dialysis process itself than of uremic intoxication.

In contrast to their heavy reliance on urea and creatinine levels in patients with progressive renal failure prior to reaching end-stage, nephrologists have found that serum levels of these compounds fail to provide a reliable index of dialysis adequacy. Instead, careful prospective investigations of morbidity and mortality, such as the United States National Cooperative Dialysis Study (NCDS), have underscored the importance of providing a minimum dose of dialysis regardless of solute concentrations in the patient [42, 30]. The dose of dialysis is expressed as a clearance, adjusted to the patient's size, of the same small molecular weight compounds (urea and creatinine) that were used with poor success in the past as markers of uremic toxicity. Minimum standards have been established for HD treatments administered 3 times per week and for continuous peritoneal dialysis (PD) [20, 21]. With respect to small solute removal, the extracorporeal synthetic membranes used for hemodialysis (HD) are presumed to function in a manner closely parallel to that of the native visceral and parietal peritoneal membrane. The following paragraphs describe the rationale and methods for quantfying, prescribing, and assessing the adequacy of both HD and PD.

Molecular Basis of Uremic Toxicity

Uremic Toxins

A wide variety of solutes that accumulate in patients with advanced renal failure are shown in Table 1 along with their respective molecular weights. The smaller solutes diffuse easily across the semipermeable dialysis membrane and are effectively removed by dialysis while some of the larger compounds are not removed at all. Some may be removed in part by adsorption to the membrane and some of the larger compounds may be removed more effectively by high flux (high porosity) membranes. Some of the compounds listed in Table 1 cause symptoms similar to those observed in uremic patients (e.g. the guanidines) but only when levels in the serum are much higher than observed in patients with overt uremia.

Alternative Theories

It is difficult to imagine that despite all the sophisticated methods of chemical separation and identification available today, and the numbers of patients available for investigation that the critical toxins have not been identified. Although existence of an elusive but dialyzable toxin remains possible, the failures of the past has spawned alternative theories to explain uremic toxicity. Many of these theories have fallen into disfavor because they fail to account for the dramatic and life sustaining effect of dialysis, which offers little more than removal of relatively small solutes and water from the blood. An attractive alternative explanation and perhaps the reason that a single toxin cannot be identified is that uremia rep-

Table 1. Compounds Known to Accumulate in Renal Failure*

Suspected Uremic Toxins	Molecular Weight
Nitrogenous end products of protein metabolism	
Urea	60
Creatinine	113
Guanidines	
Methylguanidine	73
Guanidinoacetic acid	117
Guanidinosuccinic acid	175
Others	
Peptides and proteins	
β-2 microglobulin	11,800
End products of nucleic acid metabolism	
Uric acid	168
cAMP	240
Pyrimidines	100 – 200
Condensation products of carbohydrate metabolism	
Glycosylated proteins and Amadori products	
Pentosidine	
Phenols and phenolic acids	100 – 300
Indoles	200 – 400
Furans	200
Amines	
Aliphatic (e.g. dimethylamine)	46
Aromatic (e.g. hippuric acid)	179
Polyamines (e.g. spermine)	202
Inorganic elements and compounds	
H^+	1
H_2O	18
Na^+	23
Al^{3+}	27
Mg^{2+}	24
K^+	39
Ca^{2+}	40
PO_4^{3-}	95
SO_4^{2-}	96
Others	
Hormones	
Parathyroid hormone	9500
Renin	40,000
“Natriuretic hormone”	?

*modified from reference [15] with permission from Kluwer Academic Publishers

resents the summation of multiple small sublethal effects of the solutes listed in Table 1.This theory is actually not new, as it was proposed by Homer Smith in his textbook, *The Kidney*, in 1951:

"The retention of urea itself, however, does not account for the toxic manifestations and physiological disturbances of renal failure, and the actual cause of death must be conceived as complex and possibly representing the summated action of numerous physiological disturbances, no one of which may be lethal itself and no one of which is consistently predominate in the uremic state."

Homer Smith, *The Kidney*, 1951, p 854 [61]

Accumulating evidence also suggests that the illness we call "uremia" is complex, consisting of an immediate life-threatening accumulation of small solutes, a more indolent effect of less readily dialyzed solutes, and several indirect phenomena such as the hormone deficiencies that cause anemia and bone disease [9, 25]. Included in the latter category are carbamylation of proteins due to the effects of cyanate which is predictably associated with high urea concentrations (Figure 1), and a maladaptive effect of uremic acidosis that increases protein and amino acid degradation and contributes to the loss of lean body mass [49, 50]. Since protein catabolism is an acidifiying process, the accumulation of acid has potential for inciting a vicious cycle where protein catabolism causes acid accumulation which leads to more protein catabolism. Like other isolated effects of uremia, however, accumulation of acid cannot be considered fundamental to the uremic syndrome because correction of acidosis alone is not enough to reverse it.

Regardless of the pathogenesis, the effects of uremia appear to reverse almost completely with dialysis or transplantation, especially if the renal failure is treated early. After prolonged kidney failure, irreversible effects appear such as infertility and vascular disease. Accumulating evidence also suggests that malnutrition may not be reversible, especially in older patients, if intervention with dialysis is delayed [53].

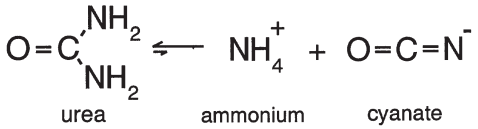

Figure 1. Urea in solution equilibrates with small amounts of cyanate. The reaction is shifted far to the left.

Surrogate Toxins: Urea and Creatinine

Enthusiasm for quantifying the severity of uremia by measuring the level of accumulated solutes has been tempered somewhat by data showing that reliance on available solute levels, such as urea and creatinine concentrations, as the sole determinant of dialysis success or failure, can be misleading and may endanger the patient. As mentioned above, serum levels are determined both by native kidney and dialyzer function and by the generation rates of each solute, which are often variable and dependent on other factors that do not correlate with the severity of uremia. Failure to include the generation rate when interpreting the level can lead to false conclusions regarding the risks of uremic intoxication and adequacy of dialysis.

Urea

Similar to the guanidines, high concentrations of urea can be associated with uremic-like symptoms such as bleeding and gastroin-

testinal disturbance, but only at concentrations above the usual clinically encountered levels [5, 36, 47, 64]. Urea stands in the center stage of the *toxic-solute/dialysis-adequacy* controversy, but its popularity has undergone wide-amplitude fluctuations over the past 3 decades. The original concept of urea as a toxin that heralded a patient's impending risk of uremia was dashed by studies in the late 1960's and early 1970's in patients with both acute and chronic renal failure, in which urea was added to the dialysate to prevent its removal by HD. The patients experienced symptomatic and objective improvement despite no change or an actual increase in serum urea concentrations [36, 47]. Following this discovery, the spotlight was turned to hypothetical "middle molecules" that were thought to mediate the uremic syndrome, but removal by dialysis was limited by their somewhat larger (middle) molecular size that decreased transport across standard dialysis membranes [4, 60]. The NCDS, however, showed that levels of urea and presumably other small solutes correlated much more strongly with patient morbidity than the time spent on dialysis, the surrogate for middle molecule removal [42] in that study. Further analyses of the NCDS data showed that the dose of dialysis correlated better than serum urea levels with outcome [30] and suggested that reliance on the urea concentration as an indicator of need for dialysis could lead to a downward spiraling vicious cycle as shown in Figure 2.

Nephrologists continue to measure urea levels in ESRD patients but the levels are used to estimate the effective small solute clearance rather than as a marker for uremia in both HD and PD patients. Guaranteeing a minimum small solute clearance is the currently accepted best method to minimize uremic complications, effectively insuring the adequacy of dialysis. Once the clearance is measured, the absolute level of urea in the serum is used as a measure of protein nitrogen appearance from which the patient's protein catabolic rate (PCR) can be calculated (see discussion below of PCRn).

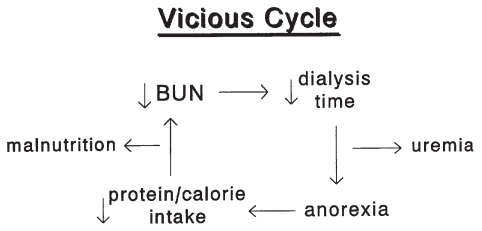

Figure 2. A potentially vicious cycle was uncovered from analysis of the NCDS data. A fall in the BUN, for reasons other than improvement in renal or dialysis function, may lead to a false sense of security as other more toxic solutes are retained.

Creatinine

The serum creatinine level is used as an index of declining renal function in patients prior to end-stage but has not proven useful for this purpose in dialyzed patients [55]. On the contrary, mortality has been correlated inversely with creatinine levels, presumably because malnutrition-related reductions in muscle mass are stronger determinants of mortality (Figure 3). Muscle mass may decline due to uremia-associated anorexia, but the fall may also be related to declining health from other comorbid conditions such as heart failure or infection [43, 52]. Although not useful in this context, serum creatinine levels are easily measured and could be used to assess effective dialyzer clearance in place of urea clearance as outlined above. However, creatinine is less diffusible than urea, develops larger concentration gradients both within the patient and across the dialyzer, and is slower to re-equilibrate when dialysis ceases. These properties of creatinine introduce more error into the measurement of dialyzer clear-

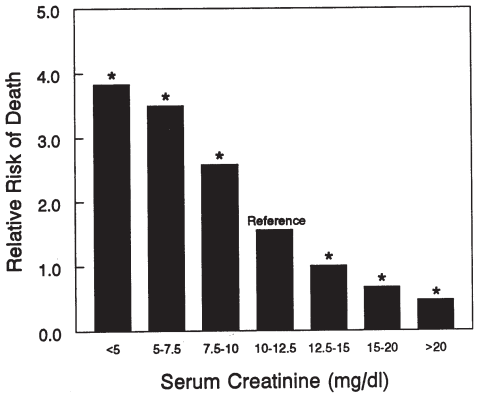

Figure 3. In a large population of HD patients (n = 19,746), serum creatinine concentrations correlated inversely with the risk of death (* $p < 0.0001$). P values refer to each group of patients compared to the reference group with serum creatinine 12.5 – 15.0 mg/dl. Adapted from reference [43] with permission from The American Journal of Kidney Diseases.

Table 2. Indicators of Prognosis

	BUN	Serum creatinine	Kt/V_{urea}
Chronic renal failure	poor	good	poor
Hemodialysis	poor	poor	good
Peritoneal dialysis	poor	poor	good

ance than similar measurements using urea. Like urea, serum creatinine concentrations continue to be measured in hemodialyzed patients, mainly to assess nutrition and muscle mass. In PD patients, solute gradients are insignificant, so the creatinine clearance continues to be used as an index of dialysis adequacy. Similar to HD, serum creatinine levels are difficult to interpret and are mainly reflective of nutrition and muscle mass.

Basis for the Prescription

Transition from Serum Creatinine to Urea Clearance

Table 2 shows the changing reliance on serum levels and clearance of both urea and creatinine as renal function deteriorates. Unlike urea, creatinine production is relatively constant from day to day and is little affected by diet. Also in contrast to urea, creatinine excretion and serum levels are unaffected by urine flow so creatinine clearance is a reasonable indicator of the GFR. For these reasons, serum creatinine levels are watched more closely than urea levels by the physician monitoring renal function in the early stages of kidney failure [55]. As renal function deteriorates further, tubular reabsorption of urea diminishes due to higher filtrate flow rates per remaining nephron, and as a consequence urea clearance more closely approximates the GFR. Despite this improved correlation of urea clearance with GFR, clinicians continue to prefer following the serum creatinine and to a lesser extent the creatinine clearance to determine the need for dialysis as the patient approaches end-stage. Once the patient becomes dependent on the dialyzer, the changing significance of serum creatinine and urea levels, as noted above, forces the physician to follow a different set of rules.

In contrast to native kidneys, artificial kidneys do not secrete or reabsorb solutes in response to volume contraction in the patient, so the serum urea/creatinine ratio loses its significance in this respect. Serum creatinine levels tend to be chronically elevated, out of proportion to urea levels, especially in males, and are disproportionately lower in patients who maintain even small levels of residual renal function. Neither urea nor creatinine

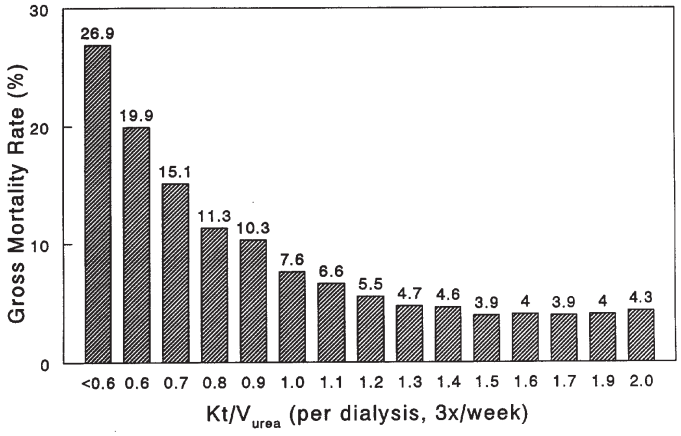

Figure 4. Mortality correlated with Kt/V_{urea} in the 1992 Japanese registry of 42,341 HD patients [62]. Gross mortality is expressed per year for the prevalent patients in each *Kt/V* category. Mortality rates for *Kt/V* values above 1.2 are not significantly different from each other. Graph adapted from reference [62] with permission from The American Journal of Kidney Diseases.

concentration in the serum is a reliable indicator of the need for or success of dialysis. One possible reason for this failure is the confinement within a relatively narrow range of artificial kidney function compared to the relatively wide range of function observed in native kidneys prior to end-stage. Consequently, the generation rate and other factors independent of dialyzer clearance (e.g. protein nutrition and muscle mass) play relatively larger roles in determining solute levels.

Both before and after intervention with dialysis, measurement of *small solute clearance* is an important part of the management of patient with renal failure. Because serum creatinine levels correlate roughly with creatinine clearance in patients with adequate native kidney function, there is less need to measure clearance. In hemodialyzed patients, both serum creatinine and creatinine clearance are difficult to interpret for reasons noted above, so soon after the initiation of HD treatments the nephrologist must transition from reliance on serum creatinine levels to reliance on *urea clearance*. For PD patients both urea and creatinine clearances are used as yardsticks for treatment adequacy, but the serum creatinine concentration cannot be used for this purpose.

Expressing the Dose of Dialysis

As noted above, morbidity and mortality rates are minimized when each patient is given a standard dose of dialysis adjusted for body size. This principle was derived from analysis of the NCDS data and subsequently confirmed by several cross-sectional studies (Figure 4) [42, 30, 52, 62]. In all of these studies, the dose of dialysis was expressed as a clearance, usually given per dialysis rather than per minute (*Kt*), and for each patient the dose was adjusted for body size (larger doses for larger patients). The index of size was not body weight but a close correlate, the volume of urea distribution (*V*), which is equated to total body water volume, usually expressed in kilograms. The adjustment for *V* was a convenient one derived from the mathematics of first order molecular kinetics (see discussion below of the *Dose Denominator*). In nearly all cases the dose is expressed not as a prescribed clearance but as a delivered clearance (*Kt/V*). The distinction between prescribed and delivered doses of dialysis is an important one that is discussed in more detail below. The combined normalization by *V* and measurement of the delivered dose from changes in blood urea nitrogen (BUN) concentrations greatly sim-

Table 3. Possible Determinants of the Need for Dialysis

Factor	Evidence
Patient size	
Weight	Correlates closely with volume
Volume	NCDS [30]
Surface area	A common scaling factor for physiologic functions
Residual native kidney function (K_R)	Mortality rates are markedly affected by K_R [11]
Gender	Males have a higher mortality rate [1]
Pregnancy	Anecdotal [32]
Diabetes mellitus	Mortality data showing that diabetics benefit more from raising the dose [12]
Urea generation rate	Old data showing improvement in uremia with dietary protein restriction without dialysis [28]

plifies the measurement and eliminates several potential sources of error.

Individualizing the Dose

The primary goal of quantifying dialysis is to assure that each patient gets enough. The implication is that patients differ in their needs according to certain identifiable and measurable parameters such as their size and/or gender. Table 3 shows a list of factors that have been considered possible determinants of the need for dialysis in ESRD patients, and are therefore candidates for inclusion in the denominator of any standard adopted for the entire population. Size and residual renal function are the most well accepted of the factors listed in Table 3 and are appropriately included in most models and standards. Although most agree that size is important, the appropriate measure of size is controversial (see discussion below of the *Dose Denominator*). Empirical data suggests that fetal outcome is improved if the dose of dialysis is increased during pregnancy [32]. Limited data have also suggested an increased need for dialysis in patients with diabetic nephropathy [12].

Mortality Rates and Dialysis Adequacy

As more experience is gained with dialysis, it is increasing clear that the amount of dialysis needed for good health is greater than that necessary to maintain life. When the amount of delivered dialysis is sub-optimal, the patient may be asymptomatic early on but the cumulative effects over a longer period of time may cause significant morbidity [30, 39]. In addition, the effects of inadequate dialysis may be difficult to reverse. Patients who were randomized to the lower doses of dialysis of short duration in the NCDS continued to show a proportionately higher mortality rate in the 12 months of follow-up after their therapy was increased, suggesting that recovery from prolonged inadequate dialysis may not always be possible with current dialysis techniques [53].

Advances in the technology of dialysis and in knowledge of the pathophysiology of ESRD over the past 3 decades have improved the quality of life for patients dependent on maintenance dialysis, but mortality and morbidity remain unacceptably high, especially in the United States [33]. For patients in the U.S.

Table 4. Hemodialysis Mortality Rates, 1987*

Country	Mean age (years)	Prevalence (per million)	Annual Mortality (%)
France	54.2	254	7.8
Japan	51.1	671	8.7
EDTA	51.6	280	10.4
West Germany	58.0	320	11.0
Australia	–	152	13.6
New Zealand	–	–	14.2
Sweden	59.0	–	14.7
Canada	54.0	186	16.9
USA	55.5	403	22.8

*adapted from reference [33] with permission from the American Journal of Kidney Diseases

initiating dialysis at age 59 years, life expectancy is approximately equivalent to the same-aged patient with a diagnosis of colon cancer [31]. In 1987, the annual mortality rate was 22.8% for all U.S. dialysis patients compared to rates of 7.8% and 8.7% reported from France and Japan respectively (Table 4). In the U.S., the mortality rate has been slightly but consistently higher in patients managed with PD compared to age-matched patients managed with HD [1]. A recently completed Canadian study of PD that included a large proportion of patients in the U.S. showed significantly worse survival in U.S. patients that was not easily explained, except perhaps by differences in patients' compliance with their dialysis prescriptions [6, 7]. In contrast to the U.S., survival of Canadian HD patients was worse than PD patients.

Self-defeating Aspects of Intermittent Dialysis

Because solute removal is the major goal of dialysis, the non-linear relationship between the intensity of dialysis and solute removal is worth examining in more detail. Doubling the dose does not double solute removal because removal depends on concentration as well as clearance and time, and the concentration falls during intermittent dialysis (Figure 5). Clearance may be high while solute removal is low. As dialyzer blood flow is increased during intermittent HD, diminishing increments in clearance are inevitable. In addition, with each incremental increase in clearance, there is less incremental removal of solute from the patient.

Causes of these additive but self-defeating effects are:

– the fundamental *first order nature of dialysis* itself due to flow and membrane-limited diffusion within the dialyzer and
– *solute disequilibrium* within the patient (see discussion below of *Solute Disequilibrium*). *Access recirculation* is a specialized case of solute disequilibrium that is separately measurable and preventable. *Cardiopulmonary recirculation* (see below) is a predictable form of solute disequilibrium found in all patients with peripheral arteriovenous shunts and absent during vein-to-vein dialysis. Differences

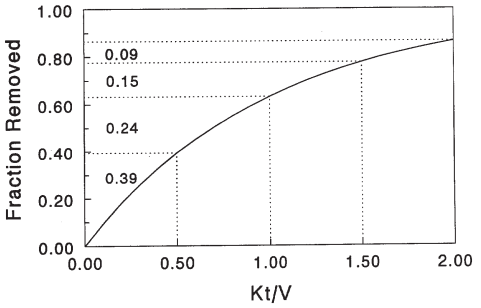

Figure 5. Single compartment analysis predicts diminishing solute removal as *Kt/V* increases from 0 to 2.0. Reprinted from reference [16] with permission from Seminars in Dialysis.

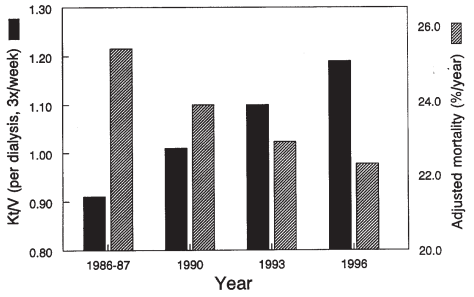

Figure 6. A slight decline in mortality among prevalent HD patients in the U.S. correlated inversely with a significant rise in Kt/V_{urea} from 1986 to 1996. Data from the USRDS [2].

in blood perfusion to tissue volume ratios cause flow-dependent disequilibrium elsewhere in the body and contribute to diminishing efficiency when attempts are made to increase the intensity of HD. Sequestration of urea in quiescent muscle is suspected to contribute to disequilibrium; support for this concept comes from a demonstrated reduction in the magnitude of urea rebound when patients exercise during HD and increase muscle blood flow [56]. Sequestration in skin has been suggested by reduction in urea rebound after warming the patient [14].

Although solute removal is increased by increasing blood or dialysate flow, the increase diminishes with each increment in flow, i.e., the two variables are not linearly related. Manipulation of blood or dialysate flow should be viewed in a proper perspective. Other maneuvers such as increasing dialysis frequency may be more effective as a means of improving dialysis efficiency (see discussion below of *Dialysis Frequency*).

Increasing Doses of Dialysis in the United States

Because the high mortality rates have raised the suspicion that patients in the U.S. have received less than the optimal dose of dialysis, the dose has significantly increased over the past 5 years. Coincident with this increase in dose, a slight decrease in mortality has been observed (Figure 6) [1]. Important remaining questions are, is the improvement in mortality related to the increase in dose and if so, how much more improvement in mortality might be gained if the average dose is increased further? Based on the above discussion about solute kinetics, one would expect that increasing the dose beyond a certain point would not further benefit the patient. At this "optimum dialysis dose", patient outcome would no longer depend on *Kt/V*. The plateau in the outcome curve is expected from a simple consideration of solute kinetics during a single dialysis treatment but it might be enhanced by an adverse effect of dialysis, e.g. by removing a vital solute or exposing the patient to a toxic solute on the dialysate side. A toxic effect of acetate, added to the dialysate as a bicarbonate base precursor, probably simulated this plateau effect in the years before bicarbonate-

based dialysate was available. Acetate is a known potent vasodilator in concentrations readily achieved during HD and was a major contributor to poor tolerance of dialysis in the past. In contrast to increasing the dose per dialysis, increasing the frequency of dialysis has better potential for enhancing the therapeutic effect of dialysis as discussed below.

Yardsticks and Mathematical Models of Dialysis

Clearance

For the nephrologist, clearance is a measure of solute removal from the body either by the native kidney or by the artificial kidney. As an expression of solute removal, clearance is more popular than the raw elimination rate because it tends to measure the process itself, independent of the serum solute concentration. This is important for intermittent dialysis where clearance tends to be constant while solute concentrations (and raw removal rates) fall dramatically and rapidly as a consequence of the dialysis. Expressing solute removal as a clearance is an attempt to normalize the removal rate for first order processes like simple diffusion and filtration, where the rate is directly proportional to (and driven by) the afferent solute concentration (*C*).

$$dA/dt = -KC \quad (1)$$

A is the amount of solute in the compartment = *CV*, i.e., the product of the concentration (*C*) and the volume of the compartment (*V*). *K* is the clearance which is constant for first order processes. If *V* is constant and there is no other addition or removal of solute,

$$dC/dt = -(K/V)C \quad (2)$$

or

$$\frac{dC/dt}{C} = -K/V = -k \quad (3)$$

Equation 3 shows that the fractional removal rate (left side of the equation) at any time during dialysis is constant despite marked changes in *C*. Clearance (*K*) is a constant like *k*, the elimination constant, but unlike *k*, is expressed as a flow. The elimination constant, familiar to pharmacokinetics, expresses solute removal rate as an instantaneous fraction of the amount available or, if *V* is constant, as a constant rate of change in fractional concentration.

Dialyzer Clearance

Dialyzer clearance (K_D) can be defined as the solute removal rate divided by the dialyzer inflow concentration and is a measure of the performance of the dialyzer. K_D is affected in a predictable manner by changes in blood flow (Q_B) and dialysate flow (Q_D), so each of these must be specified when the dialyzer clearance is given. To avoid this inconvenience when comparing dialyzers, nephrologists usually refer to the dialyzer's *mass transfer area coefficient* (K_0A) which is the maximum clearance achievable at infinite blood and dialysate flows rates. K_0A is a function primarily of the membrane since at infinite flow rates the membrane is the only barrier to clearance, which is constant for each dialyzer and solute combination. K_0A can be computed from flow rates and consideration of mass balance across the dialyzer [48].

$$K_0A = \frac{Q_BQ_D}{Q_B - Q_D} ln\left(\frac{1 - K_D/Q_B}{1 - K_D/Q_D}\right) \quad (4)$$

Recently, a positive correlation between K_0A and the dialysate flow rate has been demonstrated for a variety of hollow fiber dialyzers [41]. This additional effect (not included in Equation 4) is probably caused by channeling of dialysate (causing poor equilibration) at low flow rates that disappears at higher rates.

As defined above, dialyzer clearance, also known as *prescribed clearance*, is a real clearance that can be measured precisely from solute concentrations in blood drawn simultaneously from the inflow and outflow of the dialyzer. Because this instantaneous clearance may change during dialysis, to precisely quantify the treatment and assure that the patient received the full benefit of the prescribed dose, multiple simultaneous dialyzer inlet and outlet blood specimens would be required throughout the treatment. Fortunately this is not necessary because the *integrated clearance*, also known as the mean effective or *delivered clearance* achieved during the treatment is easily calculated from the predialysis and postdialysis BUN. However, it is important to note that the delivered clearance is a virtual clearance that is not directly measurable, so the value that is computed depends on the mathematical model of dialysis solute kinetics used to define it. The various models of urea kinetics described below define effective or delivered *dialyzer clearance*, delivered *patient clearance*, and the *continuous equivalent of intermittent clearance* (EKR).

Delivered Dialyzer Clearance: Origin of *Kt/V*

The simplest model of urea kinetics ignores urea generation and volume changes during dialysis, and provides a solution by integrating the mathematical expression of urea mass balance described in Equation 2. Integration of this equation over a period of time (t) gives a familiar expression for concentration (C) of a drug or other solutes eliminated by a first-order clearance mechanism [26]:

$$C = C_0 e^{-Kt/V} \quad (5)$$

$$Kt/V = \ln (C_0/C) \quad (6)$$

K is the integrated clearance per unit of time (t), V is the volume of distribution, and C_0 is the initial concentration. Since K and V are constant, Equation 5 expresses an exponential relationship between concentration and time. Equation 6 is simply a rearrangement of Equation 5 that demonstrates how the integrated clearance can be calculated from two timed concentrations (C_0 and C). When the integrated clearance, averaged between time zero and t, is expressed per "t" unit of time and factored by V, the clearance is expressed as "Kt/V". This expression is apparently dimensionless because the volumes cancel leaving only a fraction per unit of time. It is important to note that the time factor is not eliminated and that this expression is actually a measure of normalized or fractional clearance per dialysis and has units of time^{-1}. Since it represents a measure of the dose of a single dialysis, the schedule of dialyses must be included whenever Kt/V is given as a standard or measure of dialysis adequacy. Note also that the individual components of the expression are not actually measured; only the two serum concentrations are required.

The Meaning of *Kt/V*: Prescribed and Delivered

The now antiquated practice of following the patient's BUN as an indicator of dialysis success has been replaced by a method that focuses on the performance of the dialyzer.

Both the prescribed and the measured or delivered dose of dialysis are expressions of dialyzer clearance. The prescribed clearance is estimated from the following equation, a rearrangement of Equation 4:

$$K_D = Q_B \left[\frac{e^{K_0 A\left(\frac{Q_D - Q_B}{Q_D Q_B}\right)} - 1}{e^{K_0 A\left(\frac{Q_D - Q_B}{Q_D Q_B}\right)} - \frac{Q_B}{Q_D}} \right] \qquad (7)$$

Clearance is expressed per dialysis (K_Dt) instead of per unit of time, and to allow comparison among patients, K_Dt is adjusted for patient size, expressed as V, the patient's volume of urea distribution, resulting in the expression K_Dt/V or more simply, Kt/V. Normalizing the dose to V is analogous to normalizing a medication dose to patient weight or surface area. V can be approximated from anthropometric formulae or from the mean of several previous kinetic analyses (see *Single Compartment Model* below).

A practical point when adjusting the prescription: since both Q_B and Q_D are located within and outside of the exponential terms in Equation 7, values for Q_B and Q_D must be chosen from a nomogram or derived by iteration of Equation 9 (see below). The latter method requires a computer or programmable calculator. Despite these complexities, Equation 7 is a valuable tool for adjusting the dialysis prescription when a target K_D has been identified from measurement of the delivered Kt/V.

As described above (see *Delivered Dialyzer Clearance*) the delivered dose of dialysis, also expressed as Kt/V, is calculated from BUN measurements prior to and following a given HD treatment. The delivered Kt/V is an integrated clearance that encompasses the entire dialysis and can be considered the fraction of the patient's urea volume that is cleared per dialysis. None of the three terms that make up the expression Kt/V need to be directly measured. Thus Kt/V, although a measure of effective dialyzer performance, is actually a patient-derived parameter.

When applied to urea kinetics, the simplified expression for Kt/V in Equation 6 was derived assuming no changes in the volume of distribution during dialysis and no urea generation. Since neither of these conditions usually apply to therapeutic dialysis, Equation 6 must be expanded to include the additional variables dV and G. Addition of these terms produces a more realistic expression of the single compartment model which is discussed in more detail below.

Single Compartment Model

Because urea is a small highly soluble but uncharged molecule (Figure 1) with low binding affinity for serum and intracellular proteins, it distributes only in aqueous environments and diffuses rapidly among body water compartments. The rate of diffusion is so rapid that, for some approximations, a single space of distribution, i.e. total body water (TBW), can be assumed. Given ample time for distribution, e.g. between hemodialyses when urea accumulates at a slow constant rate, these assumptions are reasonable and single-compartment kinetic models are appropriate. During HD treatments, however, blood urea concentrations change much more rapidly, causing urea gradients to appear (see discussion below of *Multicompartment Models*). If we ignore these gradients, a single pool model for urea mass balance can be described as shown in Figure 7. The rate of change in urea content within the compartment at any moment in time (t) may be computed.

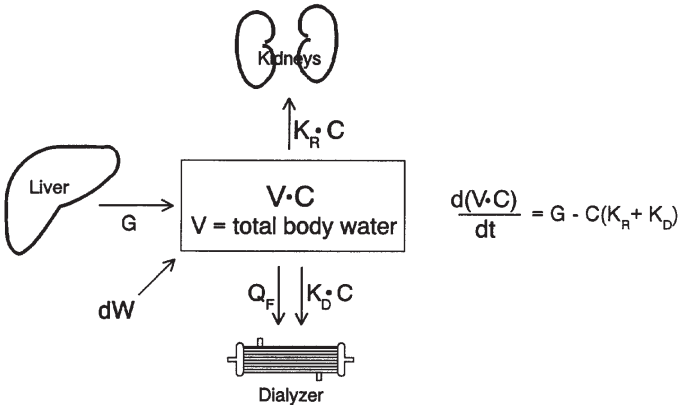

Figure 7. Single-compartment, variable-volume model of urea mass balance. K_R is the residual native kidney clearance, K_D is the dialyzer clearance, G is the urea generation rate, dW is the rate of fluid accumulation between dialyses, Q_F is the rate of fluid removal during dialysis, V and C are the volume and concentration of urea in the single pool. The equation to the right shows the determinants of an instantaneous change in urea mass balance, d(VC)/dt.

$$\frac{d(VC)}{dt} = G - KC \tag{8}$$

where V is the postdialysis urea distribution volume, C is the urea concentration, G is the urea generation rate and K is the sum of dialyzer and native kidney urea clearance (K_D + K_R). Integration of Equation 8 during and between dialyses yields the following equation for urea concentration at any time (t):

$$C = C_0\left[\frac{V - Bt}{V}\right]^{\left(\frac{K_R+K_D+B}{B}\right)} + \frac{G}{K_R + K_D + B}\left[1 - \left[\frac{V - Bt}{V}\right]^{\frac{K_R+K_D+B}{B}}\right] \tag{9}$$

where B is a constant rate of fluid gain (positive between, negative during dialyses). The modeling process begins with measured values of C and C_0 and requires fitting of V and G to Equation 9. G is determined largely from the interdialysis interval when K_D is zero while V is primarily derived from the ratio of the change in C from beginning to end of dialysis and the supplied value for K_D obtained from Equation 7. The resulting value is expressed as "spKt/V", because it is derived from a model of urea kinetics that describes the patient's urea volume as a perfectly equilibrated single pool. Sensitivity analysis shows that spKt/V is very insensitive to the selected values for K_D and the fitted value of G. For example, in a 35 liter patient with Kt/V = 1.3/dialysis and an average fluid accumulation of 1 mL/min between dialyses, as the value for K_D entered into the model varies from 200 to 400 mL/min, spKt/V changes only from 1.33 to 1.26. This simply means that the ratio of K/V is relatively constant (V is proportionate to K) and is determined primarily by the fall in BUN and time on dialysis (Equations 3 and 6).

If V can be determined independently from an anthropometric formula or from the mean of multiple previous urea kinetics modeling, then a comparison with the current modeled V determined from Equation 9 using K_D derived from equation 7 can serve as a measure of dialysis quality assurance. In general the two should agree with an error of no more than 15 – 20%. Most often, if a discrepancy is found, the computed V is larger than the expected V, indicating that the expected dialyzer clearance determined from Equation 7 was not achieved. This is usually caused by errors in blood or dialysate flow or a dialysis timing error. Other causes include loss of membrane surface area or other errors in K_0A.

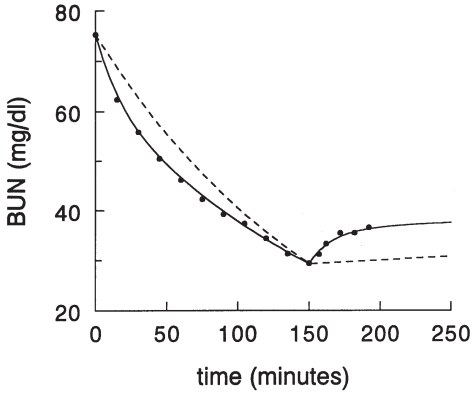

Figure 8. During the course of a HD treatment, the BUN falls in a pattern that is better predicted by a two-compartment model of urea mass balance, as shown by the solid line. The dashed line is the single compartment model prediction. Each data point is a single timed measurement of BUN in a single patient.

Solute Disequilibrium

The Single Compartment Model Fails to Predict the BUN

The assumption that TBW behaves like a single pool is incorrect. Figure 8 shows that the concentration of urea is overestimated during and underestimated immediately following a HD session. The cause of this discrepancy is a resistance to solute diffusion within the patient that causes solute gradients to develop among body water compartments during the relatively rapid removal of urea by the dialyzer. This failure to equilibrate causes the urea concentration in the blood to fall to a lower level than in the remainder of the patient, especially when compared to the intracellular space and in poorly perfused compartments such as the skin and quiescent muscle. Because the concentration of solute in the blood entering the dialyzer is the driving force for dialysis, the efficiency of dialysis falls more rapidly and to a lower level than that predicted by the single-pool model. Mathematically, the dialyzer clearance term (K_D) in the expression for single-pool *Kt/V* overestimates the average "whole body" or patient clearance.

It is important to emphasize that although the *delivered dialyzer clearance* (K_D) is usually accurate when measured using the single compartment model (see discussion below of *Single Compartment Model*), urea disequilibrium reduces the actual delivery of urea to the dialyzer by reducing the blood concentration. The lower urea concentration in blood entering the dialyzer does not lower the dialyzer clearance but reduces the amount of urea removed from the patient below what would be removed in the absence of disequilibrium. As a result, the overall effectiveness of the delivered dialysis falls below that predicted by the single-pool model.

The Single Compartment Model Accurately Predicts K_D/V

Errors in V or K_D are usually not caused by urea disequilibrium, despite the occurrence of easily documented disequilibrium (Figure 8) even during relatively low efficiency dialysis. V is not overestimated because the two major errors caused by solute disequilibrium have opposing effects on V [15]. For a delivered *Kt/V* of approximately 1.3 during a hemodialyses lasting approximately 3 hours, the errors nearly completely balance one another, giving an accurate measure of V [13, 29]. For more prolonged dialysis or less intense dialysis (lower *Kt/V*), V is slightly underestimated and for shorter or more intense dialysis, V is slightly overestimated by the single compartment model. Because of these offsetting errors, the single compartment model of HD urea kinetics serves well to measure the effective (delivered) dialyzer clearance.

The NCDS and subsequent studies showed that guaranteeing a minimum effective *dialyzer clearance* (K_D) per treatment on a regular basis in each patient minimizes individual risk from the consequences of ESRD. Because the single compartment model is simple to use and gives a reasonably accurate measure of *dialyzer clearance* per treatment factored by V (spKt/V), it has become the standard for prescribing HD and evaluating its adequacy. If the goal of kinetic modeling is to define more precisely the effect of dialysis in the patient, then additional steps must be taken to measure *patient clearance*.

Patient Clearance

Patient clearance is more difficult to define. The concept is simple and intuitive but the mathematical definition appears at first to be complex. Movement of solute from the patient to the dialysate occurs by a first-order process (diffusion), but the rates vary among tissue compartments. Patient clearance can be considered the removal rate divided by the average of all solute concentrations within the patient's tissue compartments. It is always lower than dialyzer clearance because tissue concentrations are always higher than the concentration in blood entering the dialyzer. Dialyzer clearance is a good measure of dialyzer performance, but patient clearance is a valuable measure of the overall effectiveness of the dialysis where it counts, in the patient. For example, if blood concentrations fall sharply below tissue concentrations during HD, the dialyzer clearance may be exemplary while patient clearance and removal of solute from the patient is relatively impaired.

Mean patient clearance can be measured by integrating the instantaneous patient clearances over the course of a dialysis. This would require knowledge of all tissue compartment concentrations and volumes at multiple times during the dialysis treatment. Fortunately there is a simpler technique for measuring mean patient clearance. If we ignore the multiple concentration gradients within the patient during dialysis and simply consider to patient as a black box, mean patient clearance (K_P) can be calculated from the predialysis concentration (C_0) and the final equilibrated postdialysis concentration (C_E). Assuming that following equilibration, the patient is a well-mixed solution of constant volume V, and that C_E is measured after complete equilibration among compartments, and that G is negligible, patient clearance (K_P) is (analogous to equation 6):

$$K_P = \ln(C_0/C_E)V/t \qquad (10)$$

Equilibrated *Kt/V* (e*Kt/V*)

The weakness of spKt/V as an expression of the effectiveness of HD has led to a more realistic measure of whole body or equilibrated Kt/V derived from the patient clearance also called eKt/V *or patient* Kt/V:

$$eKt/V = \ln(C_0/C_E) \qquad (11)$$

Like spKt/V, eKt/V is also a measure of fractional clearance of urea per dialysis but the patient clearance is substituted for the dialyzer clearance (K). The "e" in eKt/V denotes an equilibrated Kt/V since, as noted above, patient clearance represents the effective clearance of urea after equilibration is taken into account. eKt/V is calculated in the same way as spKt/V except that C_E is substituted for the immediate postdialysis BUN. It is worth noting that eKt/V is a virtual clearance for which there is no concrete measurable counterpart. In contrast, spKt/V is a measure of the integrated dialyzer clearance,

a clearance that may be measured directly across the dialyzer at any time during the treatment. Barring difficulty with the dialyzer or flow rates across the dialyzer, spKtV is equivalent to dialyzer clearance which should remain constant throughout the treatment.

Measuring *eKt/V*

Unfortunately, the additional time required of the patient and of the staff to obtain the one half to one-hour post-dialysis blood sample to measure C_E is prohibitive and renders this method impractical at best. The inconvenience and cost to obtain the equilibrated sample are difficult to justify. Consequently, alternative methods for measuring e*Kt/V* have been introduced that do not require waiting for solute equilibration to occur. These include collecting and measuring urea removed in a total collection of dialysate, in multiple samples of dialysate, or as a continuously recorded concentration profile; measuring multiple samples of blood during dialysis; and applying mathematical formulae to approximate e*Kt/V* from sp*Kt/V* based on parameters known to influence the magnitude of rebound. A recent comparison of these methods in a large sample of well controlled dialyses showed that a simple linear formula for e*Kt/V* based on sp*Kt/V* and the fractional rate of urea removal during dialysis (*rate method*) gave values for e*Kt/V* closest to that calculated from the equilibrated BUN obtained 30 minutes to an hour postdialysis:

$$e\mathit{Kt/V} = sp\mathit{Kt/V} - 0.60(K/V) + 0.03, \quad (K/V \text{ expressed in hours}^{-1}) \qquad (12)$$

For patients without peripheral A-V access, the relationship to *K/V* was less steep:

$$e\mathit{Kt/V} = sp\mathit{Kt/V} - 0.42(\mathit{K/V}) + 0.02, \quad (\mathit{K/V} \text{ expressed in hours}^{-1}) \qquad (13)$$

Equations 12 and 13 show that if sp*Kt/V* remains constant, e*Kt/V* will decrease as the intensity of dialysis (*K/V*) is increased or as dialysis time is shortened. These equations also suggest that urea rebound and therefore urea disequilibrium are predictable and that rebound is determined primarily by the intensity of dialysis, defined as *K/V*. A practical advantage of Equations 12 and 13 is that no additional samples of blood or dialysate are necessary since *K/V* can be determined from sp*Kt/V* and *t*. This eliminates the inconvenience to patients and the cost to dialysis facilities otherwise incurred in attempts to accurately measure either the equilibrated postdialysis BUN or dialyzer clearance. Note that to determine e*Kt/V*, sp*Kt/V* must be measured. This allows a comparison of the current single-pool standard (sp*Kt/V*) with the more accurate dose based on the patient clearance and equilibrated urea concentrations (e*Kt/V*).

Value of e*Kt/V*

Current standards are based on sp*Kt/V*, not e*Kt/V*. Only recently has the practicality of e*Kt/V* measurements been shown, and no studies have compared the relative outcome predicting powers of the two expressions of dialysis dose. Arguments against using e*Kt/V* as a measure of dialysis and of dialysis adequacy are listed in Table 5. Fundamentally, use of e*Kt/V* takes time (duration of dialysis) into consideration, granting a bit more dialysis (higher e*Kt/V*) to the patient who remains on the treatment longer with a lower clearance but with the same sp*Kt/V*. We hope that future studies will clarify the value of this additional refinement in the expression of dialysis dosage.

Table 5. Using e*Kt/V* to Measure Dialysis

Arguments against
- No standards have been established.
- The equilibrated BUN is difficult and impractical to measure.
- Dialyzer clearance has already been shown to correlate with morbidity and mortality; why complicate the measurement?
- Adjustments in the dose require a measure of dialyzer clearance, not patient clearance.
- Disequilibrium in the patient is different for every solute. Measuring eKt/V for urea does not guarantee equal compensation for the disequilibrium of other solutes that may be more toxic than urea.

Arguments in favor
- e*Kt/V* is a true measure of the effect dialysis has in the patient.
- Expressing the dose as e*Kt/V* compensates for differences in the length of each dialysis that are independent of sp*Kt/V*.
- e*Kt/V* is easily estimated from measurements of sp*Kt/V* and dialysis time.
- Conversely, sp*Kt/V* can be calculated from e*Kt/V* to allow adjustments in the dose.
- Although it does not account for the greater disequilibrium expected in other solutes, e*Kt/V* comes closer to it than sp*Kt/V*.

The Urea Reduction Ratio (URR)

The urea reduction ratio or URR has been used as a simplified measure of the dialysis dose [35, 44, 45]. URR is defined as the fall in BUN divided by the predialysis BUN and includes the most significant factor that determines *Kt/V*, the ratio of postdialysis to predialysis BUN. Although highly correlated with *Kt/V* in population studies, URR fails to reflect the actual dose received by an individual patient as shown in Figure 9. Convective losses of solute during dialysis contribute to the overall effect of the treatment but are not reflected in URR because they are not accompanied by a change in urea concentration. In fact, whenever losses occur without a change in concentration, URR is zero, as it is for continuous PD and for native kidney function. For patients undergoing intermittent HD, it is possible to receive adequate treatment when the URR is below the standard or conversely, to receive inadequate treatment when URR is above the standard. For a patient with a *Kt/V* of 1.3 and no fluid loss during dialysis, URR is 0.71; whereas if fluid loss is 10% of body weight, URR is 0.63 (Figure 9). In contrast to *Kt/V*, URR does not provide a measure of protein catabolism or residual clearance and offers no logical method for correcting a prescription that is inadequate. For these reasons, URR was not considered acceptable by the National Kidney Foundation/Dialysis Outcomes Quality Initiative (NKF/DOQI) Hemodialysis Adequacy Work Group as a measure of, or as a standard for, dialysis. On the other hand, in the absence of other measures of dialysis, URR is much better than simply following the BUN. It is also important to note that the major work associated with determining either *Kt/V* or URR is spent in collecting and analyzing the predialysis and postdialysis blood samples. Therefore URR is less of a practical simplification than a mathematical simplification.

The Solute Removal Index (SRI)

The yardsticks of dialysis discussed above are all based on the effects of dialysis on the blood concentration which can be fairly com-

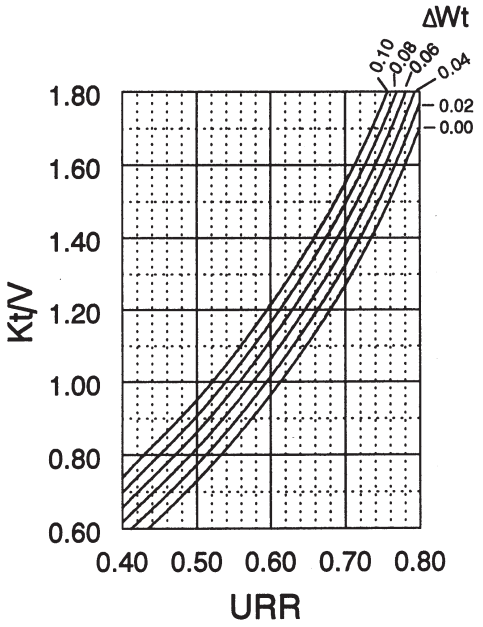

Figure 9. When *Kt/V* is constant, the urea reduction ratio varies with fluid removal during dialysis. For example, if *Kt/V* is 1.2 per dialysis, URR varies from 0.60 to 0.68 as fluid removal varies from 0 to 10% of body weight.

plex. A more direct approach that has potential for simplifying the measurement of dialysis is the method of dialysate analysis, i.e. measuring the total amount of solute removed during the treatment. If removal of urea or another solute is measured, the result can be expressed either as a clearance, i.e. the amount removed divided by the mean concentration; or, similar to the expression for URR, as the amount removed divided by the initial amount present in the patient at the beginning of the treatment. This approach is analogous to the measurement of clearance and first-order processes in general because the amount removed depends on the starting amount, other things being equal. So using the starting amount as a denominator to normalize the dose is reasonable, although not as mathematically logical as the log mean concentration used as the denominator for clearance. The dialysate method is discussed in more detail below. SRI has advantages over URR as a measure of dialysis because it includes removal of solute by ultrafiltration and residual clearance. For continuous dialysis, SRI is equal to *Kt/V*, whereas URR is zero.

Multi-compartment Models

As noted above, the patient presents a resistance to dialysis, the magnitude of which has only recently been appreciated. To more realistically model the movement of solute within the patient during dialysis and to better approximate the measured BUN levels during and immediately following dialysis, the mathematical model must be more complex than the simple single pool model shown in Figure 7. Models based on the resistance to diffusion between the blood and tissue compartments and on differences in the relative blood flow to water volume ratio among body compartments have been developed [15, 54, 57, 58].

The Classic Two-compartment Model

In Figure 10, the patient is considered to be divided into 2 pools of water, with a finite conductivity between the pools shown as K_C, the intercompartment mass transfer area coefficient. K_C has units of mL/min, similar to clearance and could be considered the patient equivalent of K_0A. This classic two-compartment model is designed with the intracellular and extracellular water pools as prototypes for the 2 compartments and the cell wall as the major, although not the only, resistance to diffusion of urea. The differential equations describing the classic two-compartment pool model are only slightly more complex than Equation 8.

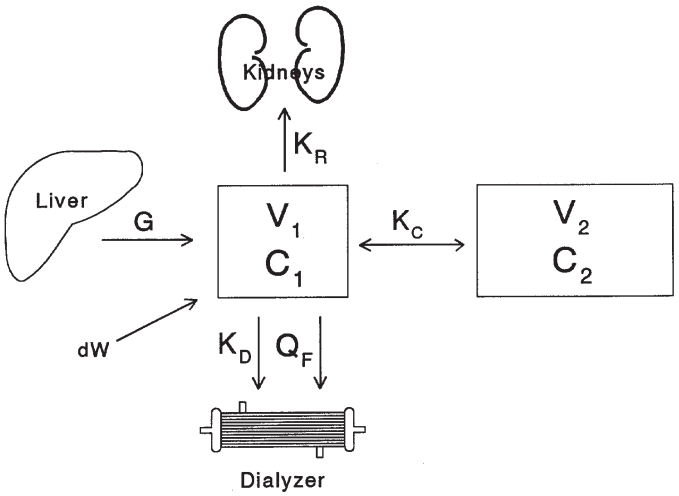

Figure 10. Two-compartment, variable-volume model of urea mass balance. In addition to the symbols shown in Figure 7, V_2 is the volume of the second (remote) compartment and K_C is the intercompartment mass transfer area coefficient. Reprinted from reference [15] with permission from Kluwer Academic Publishers.

The Convection Model and Cardiopulmonary Recirculation

More recently, a different approach, based on differential blood flow rates among body tissues, has been taken to modeling urea disequilibrium during HD (Figure 11). This model includes the component of disequilibrium due to cardiopulmonary recirculation that the classic model fails to predict, and it accounts much more precisely for the early rapid fall in BUN during HD. The overall effect on patient clearance, however, is similar and not distinguishable from the older classic model. Although the relative contributions of flow and diffusive resistance have not been quantified, it is clear that the 2 are additive. This leads one to conclude that tissue resistance to urea diffusion is lower than had been assumed in the past based on predictions of the classic model. Neither of these more complex models is currently used in clinical practice, but it is possible to simulate their effects on *Kt/V* using the rate equation (see measurement of e*Kt/V* above).

Dialysate Methods

Hemodialysis

One of the advantages of intermittent HD is the easy method it provides for measuring dialyzer urea clearance, urea generation, and the patient's volume of urea distribution with simple blood measurements without the need for collecting dialysate, i.e. without measuring what is removed. This convenience is not available to patients with continuous kidney function, either native or replacement, where collections of urine and dialysate for measurement of clearance are usually required. However, measuring changes in blood concentration requires careful timing of the postdialysis blood sample to avoid errors from postdialysis rebound and from recirculation of blood through the access device. It also requires complex mathematical interpretation and multiple blood samples if one intends to precisely account for solute disequilibrium in the

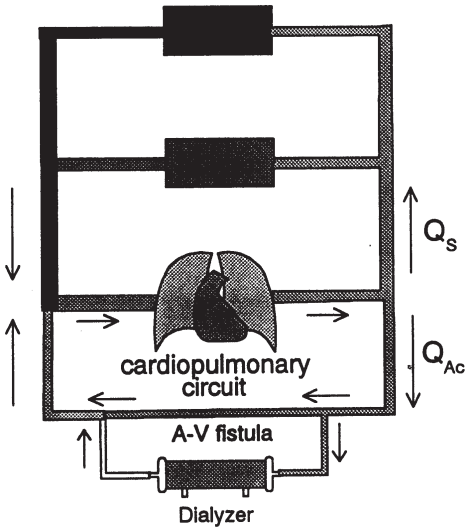

Figure 11. In contrast to the classic diffusional model of urea kinetics shown in Figure 10, this model is based only on blood flow in the patient. Gradients for urea appear in the blood compartment during HD because of differing rates of perfusion among body tissues. Even in the absence of any diffusion barriers, this model predicts a rapid fall in BUN at the beginning of dialysis and a sharp rebound following the end of the treatment. The rapidly circulating blood compartment is the cardiopulmonary circuit through the peripheral A/V access device.

patient. Measuring the dose of dialysis on the dialysate side is more direct and constrained by fewer assumptions, so there are fewer pitfalls and the results are theoretically more reliable and reproducible. Virtually all of the parameters that are measurable on the blood side are also available from dialysate methods, including K_D, V, PCRn, $K_{C,}$ and eKt/V. In contrast to blood-side methods that estimate dialysate removal, dialysate methods directly measure removal, which may then be used to estimate blood concentrations including the equilibrated postdialysis BUN. The latter estimate eliminates the necessity for drawing this problematic blood sample (see discussion below of rebound).

Because collection of the total dialysate is impractical, automated methods have been developed for measuring dialysate urea concentrations either continuously or at frequent intervals during treatment [3, 18, 24, 37]. Automated techniques for real-time monitoring of dialysate offer the clinician (and the patient) an immediate feedback, even before the dialysis is completed. On-line methods can also provide a precise delivered dose of dialysis during each treatment by adjusting the dialysis prescription concurrently. Dialysate flow is also more easily and directly measured by collecting timed samples.

To quantitate dialysis using dialysate measurements, the most logical index of adequacy is the solute removal index (SRI) defined above. To calculate SRI for urea, the dialysate urea, the predialysis BUN, and the patient's urea volume (V) must be measured. Predialysis levels can be determined by equilibrating the dialysate with the blood before starting the procedure and the patient's urea volume, which is relatively constant, can be measured infrequently from dialysate measurements:

$$V = \frac{Q_D C_D t - DVC_0 - t(G - K_R C_{AV})}{C_0 - C_E} \qquad (14)$$

where Q_D is total dialysate flow including the ultrafiltration component; C_D is the dialysate urea nitrogen concentration; C_0 is the predialysis BUN; C_E is the equilibrated postdialysis BUN; ΔV is the fluid lost during dialysis; K_R is the native kidney clearance; and C_{Av} is the log mean urea concentration during dialysis. An adjustment in the serum urea concentration is required to convert to serum water concentration. K_D may be estimated as the removal rate ($Q_D C_D$) divided by C_{Av} or from fitting a curve to multiple dialysate concentrations (Figure 12) [37]. eKt/V may then be calculated from each of its components or from a simplified equation:

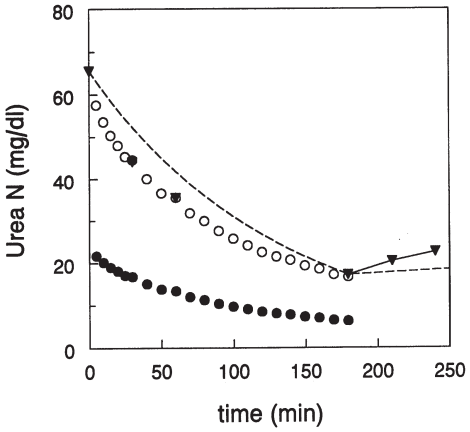

Figure 12. Urea concentration profiles in the blood and dialysate during HD. Solid circles are the measured dialysate concentrations, open circles are the calculated blood concentrations, closed triangles are measured blood concentrations and the dashed line is a prediction of blood concentrations by the single pool model. The dialysate profile may also be modeled to calculate a clearance and assess adequacy of the dialysis.

$$e\mathit{Kt/V} = -\ln(1 - \mathrm{SRI}) \qquad (15)$$

Compared to the analogous equation that uses URR instead of SRI, Equation 15 is more accurate but it also underestimates *Kt/V* when ultrafiltration occurs during dialysis. Once *V* is determined, C_E may be estimated as:

$$C_E = \frac{C_0(V + DV) - t(Q_D C_D - G + K_R C_{AV}}{V} \qquad (16)$$

Error Magnification

Compared to blood-side methods, dialysate methods suffer from an inherently larger error when used to measure the dose of dialysis because to determine e*Kt/V* they require subtraction of two relatively large quantities, the amount of urea in the patient predialysis and the amount removed. The resulting percentage error is considerably larger than usual measurement errors and gets larger as the dose of dialysis increases (high e*Kt/V*). Although the dialysate method is attractive for other reasons, both theoretical and observational data show that it can cause much larger errors in both SRI and e*Kt/V* than blood-side methods [17]. The error in e*Kt/V* is smaller when estimated on the blood side because BUN levels are directly measured both before and after dialysis. The magnified subtraction error inherent in the dialysate method can be minimized by automated techniques that measure the dialysate concentrations multiple times throughout the treatment, fitting a curve to urea concentration profile. The fitted curve allows a more accurate estimate of the amount removed as well as the equilibrated postdialysis concentration.

Peritoneal Dialysis (PD)

As noted above, quantitation of continuous dialysis modalities such as native kidney function and continuous PD requires collection of dialysate and urine. The advantageous fluctuations in urea concentration that allow simplified quantitation of HD do not occur during continuous PD, but their absence offers a clinical advantage for the patient by eliminating solute disequilibrium. The elimination of fluctuations in the BUN improves the efficiency of dialysis and also allows more simplified and unified expressions of the dialysis dose that were discussed above. For example, in patients dialyzed continuously, sp*Kt/V*, e*Kt/V*, and SRI are all equivalent and the magnified subtraction error mentioned above for SRI measured during HD is all but eliminated because of the relatively prolonged period of dialysate collection (usually ≥ 24 hours). There is no postdialysis rebound, no

cardiopulmonary recirculation, and patient clearance can be considered equivalent to dialysis clearance. Because disequilibrium is absent, creatinine clearance can be measured as easily as urea clearance and the patient's residual native kidney clearance, measured either as creatinine or urea clearance, may simply be added to the dialysis clearance to obtain the total clearance. The burden of measurement is shifted from the lab to the patient who must supervise the relatively prolonged collection of dialysate and urine, so measurements of PD are usually not performed as often as measurements of HD. Because they are collected over ≥ 24 hours, peritoneal measurements are theoretically more stable and reproducible than typical HD clearances, although this question has not been directly addressed.

Traditionally, PD has been quantified using urea *Kt/V* per week or using the weekly creatinine clearance. Either may be expressed as *Kt/V* or as an unmodified clearance but neither can be compared directly to HD clearance. Intermittent clearance cannot be compared directly to continuous clearance because of its intrinsic inefficiency that requires a larger dose to achieve the same effect. Intermittent clearance is compared with continuous clearance in more detail below (see *Dialysis Schedule*).

Importance of the Protein Catabolic Rate

In the era preceding the availability of therapeutic dialysis, restriction of dietary protein intake was the only treatment for patients with advanced renal failure [27, 28]. Maintaining caloric intake while restricting protein by prescribing diets high in carbohydrate and fat content was felt to prolong life by reducing the burden of uremic toxins, most of which were thought to originate from dietary protein. When dialysis became available, as a logical extension of the previous therapeutic policy, it was assumed that restricting protein intake should reduce the requirement for dialysis. So the apparent adverse effect of a low protein catabolic rate demonstrated by the NCDS was surprising. Although dietary protein intake was not controlled in a randomized prospective way in this study, the data suggested that it wasn't enough to control the BUN; outcome depended on how the BUN was controlled. Lowering the BUN by dialysis improved outcome whereas lowering the BUN by diet appeared to worsen outcome (Figure 1). PCRn was second only to the BUN itself as a predictor of morbidity. It was this finding that led to the current policy of ignoring the absolute level of urea and instead providing a minimum dose of dialysis, measured as a normalized urea clearance per dialysis given 3 times weekly, as the standard to assure adequacy of the treatment.

This new policy shifted the serum urea nitrogen concentrations from a potential indicator of need for dialysis to a marker for dialyzer clearance. The reliance of this quantification method on urea clearance popularized the technique of urea kinetics modeling which simplifies the measurement of effective clearance integrated over the entire dialysis. In addition to *Kt/V*, the kinetic modeling process also provided a measure of PCRn, a parameter that is important to follow because is too correlated with morbidity. Whether modifying the protein catabolic rate by dietary or other intervention will improve outcome has not been shown conclusively, but if malnutrition is the cause of a low PCRn one would expect that correcting the cause of the malnutrition would improve outcome. Often it is not

enough to simply supplement the diet with calories and protein; correcting underlying heart failure or an inflammatory state may be the more effective treatment.

Measurement of PCRn

Urea is an end-product of protein nitrogen metabolism, so its appearance can be directly translated to net protein catabolism [8]:

$$PCRn = 5420G/V + 0.17 \quad (17)$$

As shown in Figure 13, PCRn is determined mostly from the change in BUN between dialyses measured by the gradual rise in BUN during this period. On the practical side, as shown below, measurement of the third BUN is not necessary.

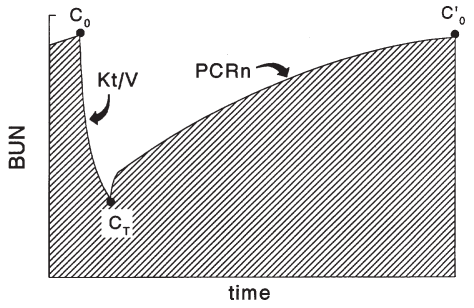

Figure 13. BUN profile during and between dialyses. *Kt/V* is determined largely from the change in BUN during dialysis while PCRn is a function of the change in BUN between dialyses but can also be derived from *Kt/V* and the absolute level of the BUN as shown in Figure 14. The shaded area represents the patient's urea exposure or time-averaged BUN.

The Two-BUN Method of Modeling

Figure 14 shows an extension of urea modeling that allows measurement of both *V* and *G* with only 2 BUN measurements. Since *V* and *G*, the 2 unknown variables in Equation 9, cannot be explicitly resolved (no single solvable equations), an iterative process is required. The two-BUN method shown in Figure 14 simply extends the iteration to cover an entire week instead of a single inter-dialysis interval. This method uses the predialysis BUN twice, first to measure *Kt/V* from the ratio of predialysis to postdialysis BUN and second to measure G and PCRn from its absolute value. The process shown in Figure 14 requires a computer, the slowest of which usually completes the resolution of *G* in under one second.

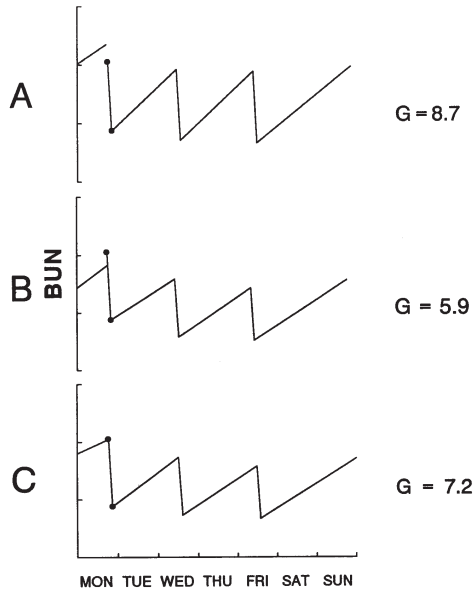

Figure 14. Two-BUN method for calculating *G*. The computer repeats the calculation of *C* for an entire week using Equation 9 and adjusts *G* until the predialysis BUN after one week of calculations matches the measured value. Reprinted from reference [15] with permission from Kluwer Academic Publishers.

Importance of the Dialysis Schedule

There is a growing interest in scheduling HD more frequently than the current almost universally applied 3 per week pattern. When intermittent dialysis is applied more often, the effects of disequilibrium are less prominent and the dialyzer is more efficient at removing solute from the patient. If the goal of dialysis is to maintain solute concentrations below a threshold level, then more frequent dialysis is better because, as shown in Figure 15, it allows a lower average clearance per week. Figure 15 also shows the effect of solute disequilibrium. As K_C, the intercompartment diffusion coefficient decreases, signifying increased resistance to diffusion, the effect of higher frequency dialysis is more prominent. Even for urea, which diffuses among body compartments with seemingly little resistance, the required *Kt/V* per week is significantly lower when dialysis is applied daily compared to 3 per week. Advances in dialysis technology have improved the dialyzer but not the resistance to diffusion in patient.

Theoretically a solute with no resistance to diffusion in the patient (infinite K_C in Figure 15) will show this effect because the dialyzer itself is more efficient when solute levels are relatively constant. Paradoxically, the inefficiency of the dialyzer is enhanced as dialyzer permeability and clearance increases. Increasing the frequency has potential for improving the efficiency of dialysis by diminishing the effects of both patient-dependent disequilibrium and the intrinsic first-order inefficiency of the dialyzer.

To allow comparison of dialysis doses among patients treated with different frequencies, a parameter known as the continuous equivalent of renal clearance (EKR) has been suggested and is discussed in more detail below under *Standards for Dialysis*.

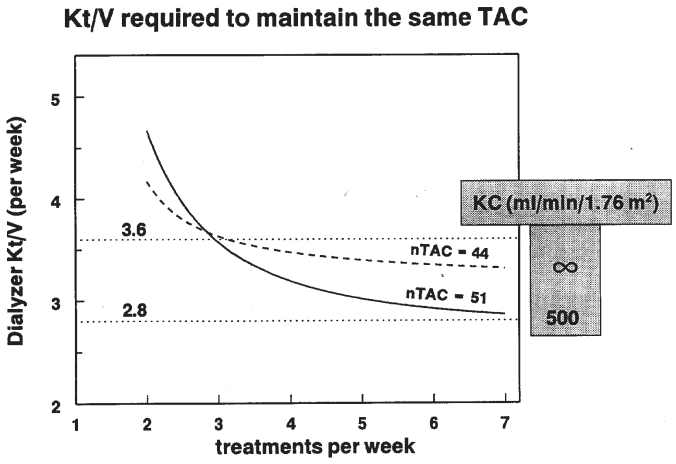

Figure 15. To maintain the time averaged BUN constant, the dose of dialysis provided per week may be reduced as the frequency of dialysis increases. The solid line shows the required weekly *Kt/V* for urea based on a K_C of 500 mL/min. Even a simple single compartment model with no resistance to diffusion in the patient (infinite K_C-dashed line) shows a dependence of weekly *Kt/V* on dialysis frequency.

Standards for Dialysis

NCDS, NIH Consensus, RPA, and NKF-DOQI Guidelines

Although the NCDS was not designed to develop standards for HD, the results permitted such an analysis. Using a mechanistic approach to the data, Gotch and Sargent concluded in 1985 that providing a minimal Kt/V_{urea} for patients thrice weekly would assure adequacy [30]. Since then the equipment and mode of delivery of HD has improved considerably allowing less strict acceptance criteria, and as a consequence the average age has increased and the patients are sicker from other comorbid diseases. Consequently, this preliminary minimum standard was revised upward to 1.2/dialysis in 1993 following a consensus development effort sponsored by the National Institutes of Health (NIH) [51]. Although no controlled data were available to support this dose, the minimum standard for HD was subsequently endorsed by the Renal Physicians Association (RPA), the National Kidney Foundation (NKF), the American Association of Kidney Patients, and several equipment vendors [6, 51, 63]. In addition, the NKF prepared guidelines for the care of dialysis patients as part of the Dialysis Outcomes Quality Initiative (DOQI) that included instructions on such issues as how to calculate the dose of dialysis, how to draw the postdialysis BUN, and how to monitor the blood access device. These guidelines also included a preliminary recommended minimum standard for PD based on several recent studies that showed a continued improvement in morbidity and mortality as the dose of dialysis increased to the 2.0 – 2.2 per week range. These guidelines were published in late 1997 [20, 21].

Standards for Different Schedules: a Universal Approach

Figure 15 shows that it is not possible to compare values for *Kt/V* among patients dialyzed at different frequencies. This variation in dialysis efficiency at different frequencies probably explains the difference in standards for intermittent HD compared to continuous PD: higher frequency dialysis (continuous can be considered an infinite frequency) is more efficient. To permit comparisons among patients dialyzed with different schedules, an index of dialysis has been developed that is independent of schedule. This parameter, the continuous equivalent of renal clearance (EKR), is conceptually simple [10]; it represents the continuous clearance required to achieve the same average solute level in the patient. EKR is also mathematically simple; it is the average solute removal rate divided by the average solute concentration, which is the classical definition of clearance. In stable patients whose urea losses are matched by their protein intake, the urea generation rate (G) can be substituted for the removal rate and the average urea concentration in intermittently dialyzed patients is the time-integrated or time-averaged concentration (TAC).

$$EKR_{urea} = G/TAC \quad (18)$$

PCRn can be substituted for G using Equation 17 and time can be stretched to a week to give the weekly equivalent of Kt/V_{urea}:

$$EKRn = 10.08(PCRn - 0.17)/(5.42\ TAC) \quad (19)$$

where EKRn is the normalized EKR expressed as a fraction of V per week. Both G (or PCRn) and TAC are calculated from formal urea kinetics modeling but are not easily obtained by other means. EKR can be expressed either in terms of Kt/V (a fractional or normalized clearance) as in equation 19 or as a conventional clearance expressed as vol-

umes per unit of time (e.g. mL/min) as in Equation 18. As calculated using either Equation 18 or Equation 19, EKR is a total clearance that, like continuous clearance, can be broken into its constituents, residual native kidney clearance (K_R) and dialyzer clearance (K_D), by simple subtraction. For example, if EKR_{urea} is 12 mL/min and KR is 3 mL/min, the dialyzer contributes 9 mL/min. Expressed as a normalized clearance, if EKRn is 2.0 per week, and residual clearance is 0.6 per week, then the dialyzer contribution is 1.4 per week. These simple additions and subtractions are not possible with either sp*Kt/V* or e*Kt/V* for intermittent dialysis.

The single compartment model overestimates *G* and underestimates TAC, causing an overestimation of EKR as calculated using Equation 18. Therefore, to calculate EKR accurately from values for *G* and TAC provided by formal urea modeling, consideration must be given to disequilibrium using a two-compartment approach. The *rate equation* (Equation 12 or 13) can be used to make the downward adjustment in *Kt/V* from which Ceq, TAC, and *G* can be recalculated. Using the rate equation for this purpose is justified if the duration of dialysis and clearance are comparable to thrice weekly schedules (e.g. 2 – 4 hours, 200 – 300 mL/min in an average-sized adult).

For intermittent dialysis, EKR is always lower than the patient clearance (e*Kt/V*), the difference representing the efficiency of continuous compared to intermittent scheduling. However, if one compares the current minimum standard clearance for PD (Kt/V_{urea} = 2.0 – 2.2/week) to the consensus-derived minimum standard clearance for HD (Kt/V_{urea} = 1.2/dialysis, thrice weekly), adjustments for urea disequilibrium and inefficiency of intermittent dialysis do not completely explain the discrepancy. EKRn, even when the proper adjustments are made for disequilibrium, is approximately 2.8 per week in a patient whose HD provides a urea *Kt/V* of 1.2/dialysis, thrice weekly. Although 2.8 is closer than 3.6 (3 × 1.2) to the 2.0 – 2.2 range targeted for PD, it remains significantly higher. A possible explanation for this discrepancy is that urea exhibits less disequilibrium than the average real uremic toxin.

Although EKR is attractive as a universal expression of dialysis dose, at the current time there are no standards for EKR and regulatory agencies in the U.S. currently demand either *Kt/V* or URR to document dialysis adequacy. Another potential problem with EKR is the lack of an easy method for correcting a dialysis dose that does not meet the target. Conversion to sp*Kt/V* is required to allow changes in the dialyzer clearance or time.

Since EKR is a continuous function, it can be compared directly to native kidney function in a patient prior to initiating renal replacement treatments for ESRD. The benefit of supplemental dialysis can be compared to the patient's dwindling native kidney function and a more rational plan developed for timing the intervention. Population studies of EKR may shed more light on the optimal time to initiate dialysis.

The Denominator for Expressing the Dose of Dialysis

Table 3 shows several currently recognized and suspected factors that modulate the need for dialysis. Expressing the dose as *Kt/V* and establishing a standard based on this value essentially ignores the other potential factors listed in this table and others that may not be listed. *Kt/V* can be adjusted for K_R using several suggested methods, including the EKR method mentioned above, but among the other factors listed, only size is included in *Kt/V*. Patient size is a logical denominator, as

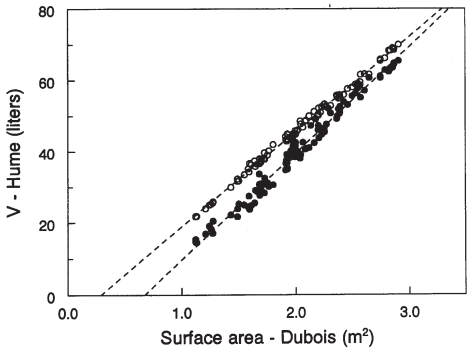

Figure 16. The Hume formula for total body water correlates closely with surface area but differs for men and women. For a given surface area, men (open circles) have more water volume than women (closed circles) [22, 34]. Random data generated using heights 120 – 220 cm, weights 30 – 150 kg.

larger patients are expected to require a higher clearance, analogous to native kidneys, but the appropriate index of size remains controversial. The use of *V* as a denominator is simply a mathematical convenience that, because it correlates strongly with many other size dimensions such as height, weight, and surface area, is probably close to if not an exact match to the most appropriate size denominator. In a patient with constant *G*, however, *V* has little effect on the steady-state solute concentration as shown in Equation 18. A logically more appropriate denominator of size is *G*, the toxin generation rate, not to be confused with urea generation (G_{urea}). Current evidence suggests that *G* is more closely correlated with surface area than with *V*. If this reasoning holds true then we may have to make adjustments to *Kt/V* based on surface area to volume ratios as shown in Figure 16.

Adjusting *Kt/V* for K_R is logical but is rarely done. Most nephrologists prefer to begin dialysis with a dose that is more than adequate to avoid future stepwise increments, usually translated to the patient as an increase in time on dialysis, and interpreted negatively by the patient. If K_R is not measured and ignored in the prescription of *Kt/V*, the patient will be protected from underdialysis but outcome comparisons among patients will not be possible.

Practical Application and Pitfalls of Urea Modeling

The last 2 decades of experience with urea modeling have uncovered a number of pitfalls, most of which can be easily avoided. Usually these problems surface when the results of a patient's urea kinetics analysis do not meet expectations or deviate from previous results (see *Troubleshooting* below). One of the most common sources of error in hemodialyzed patients is in the method for obtaining the post-dialysis blood sample.

When to Draw the Post-dialysis BUN and Why

When drawing the post-dialysis blood sample, care must be taken to avoid artifacts from dilution of the sample with intravenous fluids (saline, blood, and other solutions), often given near the end of the treatment, or from local access recirculation. Care must also be taken to avoid rebound which may begin less than 10 seconds after stopping the blood pump. The instability of the post-dialysis BUN due to these influences necessitates precise timing of the sampling within a short window measured in seconds to minimize errors in the modeled parameters including *Kt/V*. Unless an equilibrated sample is sought, the blood should be drawn at the precise end of the dialysis but precautions must be taken to eliminate the potential effects of access recirculation. Both access recirculation and

rebound artifacts can be minimized by first slowing the blood pump to approximately 100 mL/min and then waiting ≥ 10 seconds but not > 20 seconds to draw the sample. To avoid haste and possible injury from needles used to draw the sample, the blood pump may be stopped after waiting the 10 – 20 second interval, and a sample drawn more leisurely from the arterial (dialyzer inflow) port. If access recirculation exists and the sample is drawn at full blood flow, the postdialysis BUN will be too low, giving the false impression that the patient is receiving more dialysis than is really the case; this will endanger the patient. If sampling is delayed too long (> 20 seconds after slowing the pump), the postdialysis BUN will be too high, in some cases giving the false impression of too little dialysis. Although this will not endanger the patient, it will cause inconvenience and inability to correlate dosage with outcome. If the blood tubing used in the dialysis center is the same from patient to patient, the volume of the tubing from the tip of the needle to the sampling port (usually 5 – 9 mL) can be measured. A volume of blood equivalent to 1.5 times this volume should be washed past the sampling port after slowing the blood pump and before sampling (e.g. if the volume is 8 mL, the pump can be stopped after seconds).

Troubleshooting

To measure dialyzer clearance and the patient's volume of urea distribution, blood flow rates must be accurate, but standard blood pump meters that rely on the pump's rotational speed (RPM) are subject to error. Imprecise calibration of the pump and low pre-pump pressures contribute to errors when *V* is measured on the blood side but not when *V* is measured on the dialysate side [19]. Conversely, when urea concentrations are measured on the dialysate side, proper calibration of the dialysate pump is essential. In addition to the causes of real reductions in dialyzer clearance listed in Table 6, an apparent reduction in clearance may be caused by overestimation of the dialyzer K_0A obtained from the manufacturer's specifications which may be based on saline dialysis instead of whole blood dialysis. False reductions in *V* or false elevations in G are encountered less often than their counterparts listed in Table 6. Modeled *V* may be too low if the postdialysis BUN is falsely low due to dilution as discussed above (*When to draw the post-dialysis BUN*). *V* may also be too low if the dialyzer K_0A is underestimated or if modeled dialysis time is less than the actual time. PCRn will be falsely elevated if either *V* or residual clearance is overestimated.

The Future

As HD equipment becomes safer to use and the treatment is better tolerated, the focus of development efforts will be turned more toward assuring adequacy. For intermittent dialysis as well as continuous dialysis, patient outcome ultimately translates to a sustained reduction in tissue levels of toxic solutes while the dialyzer effectiveness is essentially a measurement of clearance. Since we have not identified the key solutes to measure in the patient, we are left with measurement of dialyzer urea clearance, factored for body size, as a surrogate for this highly sought but currently unreachable goal. Medical science has hopes of uncovering the identity of the critical toxins and their mechanisms of toxicity that should help as a guide to more rational dialysis therapy in the future. Population studies may give

Table 6. Common Problems Uncovered by HD Urea Modeling

Potential causes of reduced clearance (high V)
– Malfunction of the blood or dialysate pump
  Low pre-pump pressure [19]
  Poor occlusion of pump head rollers
  Wrong blood pump segment
  Blood or dialysate pump calibration error
– Faulty dialyzer
  Clotting (inadequate anticoagulation during dialysis)
  Reused dialyzer, not terminated appropriately
  Channeling of blood or dialysate flow [41]
  Co-current rather than countercurrent flow of blood/dialysate
  Manufacturing variance
– Access recirculation
  Low access flow rate
    Peripheral A/V access: stenosis due to neo-intimal hyperplasia
    Central venous catheter access: short femoral catheter [40]
  Reversal of needles or catheters
  Close approximation of needle tips
– Blood sampling or measurement error (e.g. false elevation of post-dialysis BUN due to rebound)
– Error in timing: modeled time on dialysis greater than actual time
– Intradialysis parenteral nutrition (IDPN) causing transient elevation of G during dialysis [46]

Potential causes of low PCRn
– Low dietary intake of protein (anorexia, starvation, excessive protein restriction)
– Anabolic states
– False contraction of *V*
– Underestimation or failure to include residual clearance in the modeling
– Blood sampling or measurement error (e.g. drawing the predialysis BUN after starting the blood pump)

clues to the source and identity of toxic solutes and to resolve the question about appropriate denominators for normalizing the dose among patients at risk. The standards that are currently applied deserve continued scrutiny and refinement especially with regard to patients on the fringes of the normal distribution of known risk factors and perhaps others at risk from yet unidentified factors.

Because some of the answers to these questions are of national importance, the U.S. Division of Urologic and Hematologic Diseases (DKUHD) of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) initiated a clinical trial, called the HEMO Project, in 1994 to examine and evaluate HD treatment regimens with the hope of reducing morbidity and mortality [23]. This study which will be completed in the year 2001, or perhaps before this if a significant benefit is seen, is designed to test the effect of dialysis dose and membrane porosity on patient outcome.

The more immediate future holds promise for expansion of dialysate methods, including real time feedback of dialyzer clearance, and other on-line technologies to guarantee the adequacy of each treatment. Recent concerns about the inefficiency of infrequent HD has underscored the advantages of daily dialysis. Technical advances in delivery systems on the horizon may allow HD to be administered more frequently with assistance from telemedicine and home monitoring.

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