
Core Curriculum

Hemodialysis adequacy: Basic essentials and practical points for the nephrologist in training

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INTRODUCTION

The seemingly miraculous effect of therapeutic hemodialysis that sustains life indefinitely was surprising to early investigators. That a complex organ like the kidney could be replaced by simple diffusive removal of solute from the blood was both impressive and educational to those involved in its development. Hemodialysis allowed life to continue and patients to prosper even after total loss of the kidneys, for example, after surgical removal, an event that was routinely followed by uremic death usually within a few days in previous animal studies. The effect of a single dialysis was often dramatic, awakening a comatose patient near death from uremia. Today we know that total kidney replacement requires more than just dialysis, but we also know that a minimum amount of dialysis is required to optimize both the duration and the quality of life. This article will focus on the prescription of dialysis itself, including methods of measuring the dose and expressing it in a way that best reflects its therapeutic effect.

Quantifying acute and chronic kidney failure

Measurements of dose have been applied to treatment of both acute and chronic renal failure, but the most

precise relationships between dose and outcome have come from studies of relatively stable patients who require indefinite renal replacement, a population that now numbers more than 1.4 million people worldwide.^{1,2}

Uremia

Uremia, the clinical syndrome resulting from kidney failure, is a toxic state attributed to accumulation of solutes normally excreted by the kidney. This syndrome, which literally translates to “urine in the blood,” is the target of hemodialysis. The relationship between the syndrome and kidney disease was not obvious to ancient physicians, and even after the relationship was known, one could postulate that loss of nonexcretory functions of the kidney might play the dominant role in its pathogenesis, especially because urine volume usually does not decrease and urine content is unchanged as the disease progresses. More than a century ago, investigators found elevated serum concentrations of solutes like urea that are normally found in urine. This confirmed suspicions of an accumulation disease, but it was not until dialysis reversed the syndrome that this hypothesis could be considered proven. Similar to fulfilling Koch’s postulates, we can conclude that immediate life-threatening aspect of uremia is a toxic state caused by small-molecule accumulation because it is reversed by a process that removes small solutes. Diffusive removal of small solutes across a semi-permeable membrane is the major therapeutic effect of hemodialysis.

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Classification of retained (uremic) compounds³

Retained (uremic) compounds can be classified as

- Small solutes;
- Large solutes;
- Protein-bound substances; and
- Sequestered solutes.

Mechanisms that have been identified for native kidney removal include excretion of intact molecules by glomerular filtration and/or tubular secretion and metabolic degradation within the tubular cells. Degradation as an alternative to excretion of intact compounds is a common elimination pathway for small filtered peptides that are reabsorbed across the tubular epithelium by complex carrier-mediated mechanisms and then hydrolyzed by lysosomal enzymes within the tubular cells. Secretion is especially important for protein-bound substances like hippurate or indoxyl sulfate that have limited potential for filtration and may have limited water solubility (e.g., fatty acids).^{4,5} The artificial kidney is most successful in eliminating small unbound solutes that, judging from the success of dialysis, are the most toxic.

Dialyzer construction and function

- The essential component of all hemodialyzers is its semipermeable membrane.
- The membrane separates plasma solutes based on molecular size.
- Diffusive movement across the membrane is directly proportional to the solute concentration gradient across the membrane (from blood to dialysate).

Although toxin removal is the major effect of dialysis, removal of any particular toxin or surrogate toxin by the dialyzer is a poor measure of its function because the removal rate depends on the serum concentration. In a steady state of intake and output, the removal rate is simply a measure of the generation rate, which is independent of dialysis. The ultimate goal of dialysis is to lower the concentrations of toxic solutes in the patient, but use of solute concentrations as a measure of dialyzer effect is also confounded by variable generation rates. This problem is well demonstrated in the patient dying from uremia but with a relatively low blood urea nitrogen (BUN) because of poor protein intake. These measurement problems have been solved by substituting dialyzer clearance as an indicator of dialysis effect. Solute

clearance is not confounded by generation or nonrepresentative solute concentrations, and because it is a measure of dialyzer function, which is only indirectly (inversely) related to toxicity, the substance measured does not have to be toxic.

Properties of an ideal clearance marker

An ideal clearance marker

- Is easily measured;
- Accumulates in uremia; and
- Is easily removed by the dialyzer.

In the patient with end-stage renal disease, urea fits these requirements best. Regardless of future studies that might shed better light on specific solutes responsible for uremic toxicity, we can continue to use urea as a marker solute because it measures dialyzer clearance, not toxicity. The connection between clearance and toxicity is provided by extensive past experience with therapeutic dialysis in reversing uremic toxicity. The many unsuccessful attempts to isolate a single uremic toxin over the past 50 years suggest that a single solute unlikely accounts for uremic toxicity and that a single solute will unlikely dominate as a toxin. This means that multiple solutes, probably among the several hundred compounds found in normal urine, account for the multisystem derangements of uremia. Therefore, any attempt to correlate a single solute concentration with uremic toxicity will probably encounter the same problem that has been repeatedly shown with urea concentration as an indicator of toxicity. The National Cooperative Dialysis Study (NCDS) taught us to use the clearance of urea rather than its concentration in the blood as an indicator of dialysis success or failure and to predict patient outcome.⁶

Dialyzer performance: clearance

- Clearance is the ratio of removal rate to blood concentration, a solute-specific measure of the dialyzer's effectiveness (K is the symbol for clearance).
- As the dialyzer blood and dialysate flow rates increase, solute clearance increases, but at a diminishing rate.
- The dialyzer mass transfer area coefficient (K_0A) is the maximum clearance achievable for a particular solute at infinite blood and dialysate flow rates.

Clearance and dialysance

Dialysance is a more robust expression of dialyzer potential than clearance because it accounts for accumulation

of solute in the dialysate compartment. The denominator in the clearance expression is the blood or serum concentration (C), whereas the denominator in the dialysance expression is the concentration gradient from blood to dialysate ($C - D$), where D is dialysate concentration:

- Clearance = removal rate/ C ; and
- Dialysance = removal rate/ $(C - D)$.

For single-pass dialysis, clearance and dialysance are equal, so clinicians tend to use the more familiar term "clearance." In a stagnant solution of serum allowed to equilibrate with dialysate across a semipermeable membrane, the clearance of a permeable solute falls with time, approaching zero as the concentrations equalize. Dialysance, however, remains constant, equal to the initial clearance when the dialysate concentration was zero. To assess the potential of a dialyzer to remove a solute found on both sides of the membrane, for example, sodium, dialysance is a more appropriate measure. An online "clearance" monitor that measures the dialysance of sodium is currently available for assessing hemodialyzer function.^{7,8}

Measuring the instantaneous clearance

The removal rate can be measured instantaneously by sampling blood on either side of the dialyzer and multiplying the difference by the inflow rate. Clearance is the removal rate divided by the inflow concentration (see above).

$$Kd = Qb_w(C_{in} - C_{out})/C_{in}, \quad (1)$$

where Qb_w is blood water flow, C_{in} is the inflow concentration, and C_{out} is the outflow concentration. Ultrafiltration must be turned off for at least 5 min before sampling from the dialyzer's inlet and outlet blood lines.

Note that clearance can also be defined as the product of the inflow rate and the extraction ratio $[(C_{in} - C_{out})/C_{in}]$, which is a dimensionless parameter (ER). When extraction is complete (e.g., urea extraction from blood flowing slowly through a hemodialyzer), the clearance is equal to the blood flow rate. Note that that clearance cannot exceed the inflow rate and that the distribution of the solute in whole blood, which may or may not include the red cells and/or the nonaqueous components of the blood, can be ignored for calculation of ER because the distribution fraction in the numerator is equal to that in the denominator. When expressing the clearance,

however, one must be careful to specify the nature of the inflow, for example, as whole blood clearance, plasma clearance, or blood water clearance. For a solute like phosphate that does not distribute in red cells, the whole-blood clearance is much lower than the simultaneously measured urea clearance, but the plasma clearance is similar in magnitude to plasma urea clearance for modern highly permeable dialyzers.

Measuring the mean (integrated) clearance during a single dialysis (Kt/V)

The instantaneous clearance is easily measured as described above, but it provides a measure of dialysis at only one point in time. The effectiveness of an entire treatment that takes place over several hours is best measured from the fall in solute concentration from before dialysis (C_0) to after dialysis (C).

As noted above, clearance is a measure of a solute's fractional removal rate, which for convection or single-pass diffusion tends to remain constant despite the marked decrease in concentration during dialysis.

$$(dC/C)/dt = -k = -K/V \text{ (if } G, dV = 0), \quad (2)$$

where k is the rate constant (fractional removal), K is the clearance, and V is the volume of solute distribution.

A constant fractional removal rate means that the absolute removal rate is proportional to the concentration, a concept illustrated in Figure 1. This graph shows that the curvilinear downward decrease in concentration with time becomes a straight line when the concentration is expressed as a logarithm. This plot might depict concentrations of a drug after intravenous injection into a simple single-compartment system with a single rate constant (k). The slope of the straight line (logarithm) in Figure 1 is $-k$ or $-K/V$. The volume (V) is assumed to remain constant during the time interval depicted.

Integration of Equation 2 yields

$$C = C_0 e^{-Kt/V}. \quad (3)$$

Rearranging,

$$Kt/V = \ln(C_0/C). \quad (4)$$

Equation 4 is a fundamental expression that allows measurement of clearance when blood concentrations change during dialysis, but it is also oversimplified, primarily

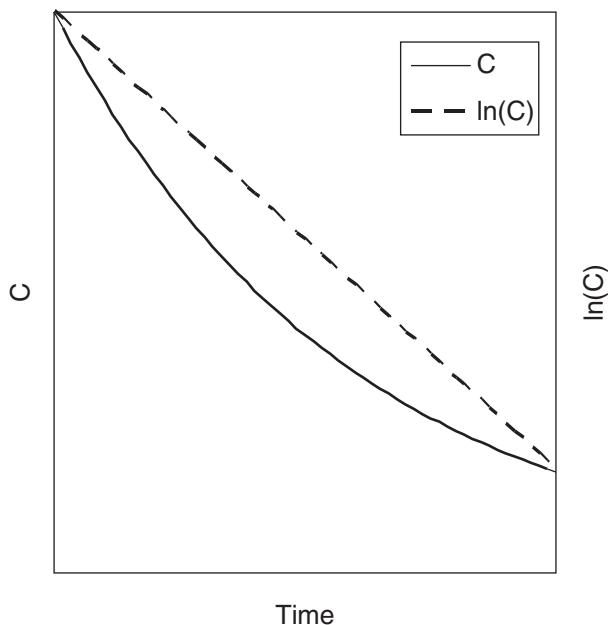


Figure 1 The curvilinear decrease in solute concentration with time on dialysis becomes a straight line with slope equal to $-K/V$ when plotted on a logarithmic scale.

because it does not account for the change in V because of ultrafiltration that occurs during nearly all therapeutic hemodialysis procedures (adding 10%–30% more to clearance), and to a lesser extent because it does not account for the generation of solute that occurs during a 3- to 5-hr treatment. To include these additional factors, one must consider a more complete description of mass balance.

Urea mass balance

A single well-mixed pool of urea is shown in Figure 2 as a central rectangle containing an amount of urea equal to the concentration (C) multiplied by the compartment volume (V_{urea}), which is equated to total body water. Urea enters the compartment only from the liver where it is generated from amino acid catabolism (G). Removal occurs constantly through the patient’s native kidneys with clearance K_r and intermittently through the dialyzer with clearance K_d . Total clearance (K) is the sum of K_r and K_d during dialysis and equal to K_r alone between dialysis procedures. The rate of change in the compartment’s urea content, $d(V_{\text{urea}}C)/dt$, is the difference between the generation rate (G) and the removal rate ($-KC$), analogous to Equation 2:

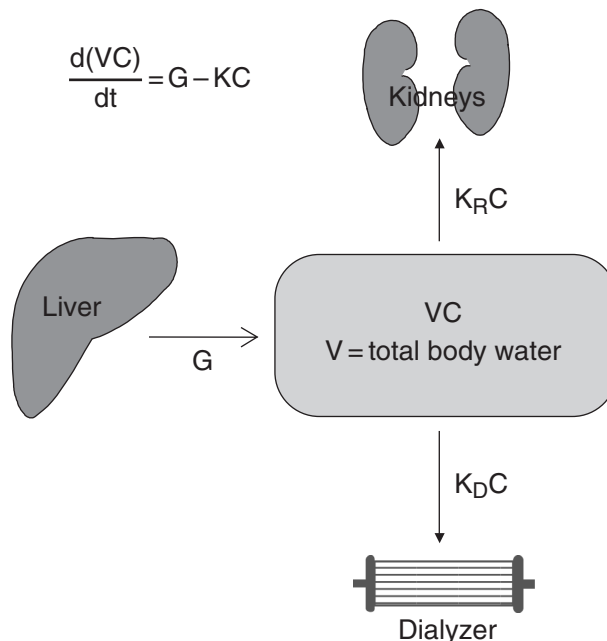


Figure 2 The single-compartment model of urea mass balance. VC is the amount of urea in the patient, the product of the urea concentration (C) and the patient’s volume of urea distribution (V), which is assumed to be well mixed throughout the dialysis. The differential equation at top left describes urea mass balance at any moment in time as the result of urea generation (G) minus removal (KC). See text for a more detailed explanation.

$$dCV_{\text{urea}}/dt = G - KC. \tag{5}$$

Integration of Equation 5 produces an explicit but much more complicated version of Equation 3.^{9,10}

$$C = C_0 \left[\frac{V_{\text{urea}} - B \cdot t}{V_{\text{urea}}} \right]^{\left(\frac{K+B}{B}\right)} + \frac{G}{K+B} \left[1 - \left[\frac{V_{\text{urea}} - B \cdot t}{V_{\text{urea}}} \right]^{\left(\frac{K+B}{B}\right)} \right], \tag{6}$$

where V_{urea} is the postdialysis urea distribution volume (mL) and B is the rate of change in V_{urea} (mL/min), which is negative during dialysis and positive between dialysis procedures.

Equation 6 cannot be reduced to a single equation like Equation 4, but it can be used to determine clearance by iteration using a computer or programmable calculator. This process, called “urea modeling,” calculates the delivered dose of dialysis as the single-pool Kt/V_{urea} ($\text{spKt}/V_{\text{urea}}$).

Formal urea modeling

Urea modeling is an inverse application of Equation 6. From measured predialysis and postdialysis urea

concentrations the constant variables G and K/V_{urea} are resolved by iteration using a programmable calculator or computer. In addition to calculating Kt/V_{urea} , if V_{urea} is known, modeled (delivered) K can be compared with prescribed K to troubleshoot the dialysis process. The prescribed K is determined from Equation 8, described below. Solution of Equation 6 by urea modeling is analogous to the explicit solution of Equation 4 and provides a measure of Kt/V_{urea} , the dialyzer clearance (K) integrated over the entire treatment time (t), factored for the patient's size (V_{urea}).

Use of V_{urea} in the denominator of the urea clearance expression (Kt/V_{urea}) is analogous to correcting creatinine or iothalamate clearance for body surface area (BSA). Use of V_{urea} instead of BSA is a mathematical convenience, as the above derivation shows. V_{urea} is closely associated with lean body mass, because muscle mass is highly represented by V_{urea} and adipose tissue contains much less water. Biologic processes, however, including glomerular filtration, tend to correlate better with BSA than with body mass, so some investigators have proposed further correction of Kt/V_{urea} to account for the differences between lean body mass and BSA. The reader is referred to other sources for further discussion of this issue.^{11,12}

Another advantage of formal urea modeling is the ability to calculate the urea generation rate (G) from which the patient's net protein catabolic rate can be determined as an index of nutrition. Like K/V_{urea} , G is a uniquely quantifiable variable made available by the perturbations in urea concentration caused by intermittent dialysis. G is determined primarily from the rise in urea concentration between dialysis treatments in accordance with Equation 6. Because net protein catabolism is the major source of urea, conversion to protein catabolism is straightforward:¹³

$$\text{PCRn} = 5420/V_{\text{urea}} + 0.17, \quad (6a)$$

where PCRn is the normalized protein catabolic rate in g/kg/day and G is the urea generation rate in mg/min. PCRn is normalized to an ideal body weight where V_{urea} is 58% of the weight in kg.

Dialyzer mass transport coefficient (K_0A)

As blood and dialysate flow rates increase, the clearance increases in a curvilinear fashion that eventually reaches a plateau as shown in Figure 3. This maximum clearance at infinite blood and dialysate flow rates is the dialyzer mass transfer area coefficient (K_0A), sometimes called the intrinsic clearance of the dialyzer for the measured solute

(usually urea). It is a property of the solute and of the dialyzer and is independent of flow rates and concentrations, so it is often used to compare different dialyzers and dialyzer models. K_0A is directly proportional to dialyzer membrane surface area, which is proportional to the length and number of fibers in a hollow-fiber kidney, and it is also inversely proportional to the average length of the pathways (pores) in the membrane that allow diffusion. K_0A can be measured as a function of clearance and flow rates of blood (Q_b) and dialysate (Q_d) using an equation that can be derived mathematically for countercurrent flow:^{14,15}

$$K_0A = \frac{Q_b \cdot Q_d}{Q_b - Q_d} \ln \left(\frac{Q_d(Q_b - K_d)}{Q_b(Q_d - K_d)} \right), \quad (7)$$

Clearance is usually measured instantaneously from pre- and postdialyzer blood concentrations as described above. From knowledge of the dialyzer's K_0A , the expected clearance can be calculated from a rearrangement of Equation 7 at any dialysate and blood flow:

$$K_d = Q_b \left[\frac{e^{K_0A \left(\frac{Q_d - Q_b}{Q_d Q_b} \right)} - 1}{e^{K_0A \left(\frac{Q_d - Q_b}{Q_d Q_b} \right)} - \frac{Q_b}{Q_d}} \right], \quad (8)$$

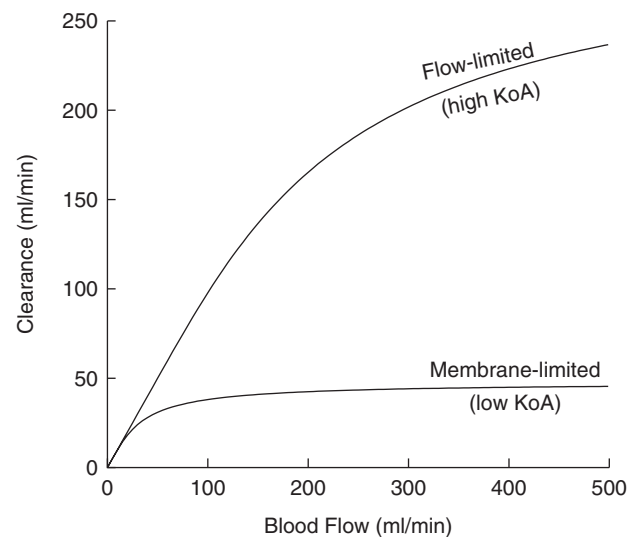


Figure 3 Solute clearance depicted in the top curve is limited more by delivery (flow) of solute to the membrane than the membrane itself. The plateau effect of flow depicted in the bottom curve indicates a ceiling imposed by limited membrane permeability to the solute. The top curve will also eventually reach a plateau but at a much higher flow rate.

Equation 8 is often helpful to calculate the prescribed or predicted Kt/V_{urea} at achievable flow rates for the particular patient, blood access device, and dialyzer. As noted above, discrepancies between the predicted clearance and the modeled clearance can point to problems with delivery of dialysis, for example, owing to access recirculation or a defective dialyzer. This exercise constitutes a quality assurance maneuver that can be used to target patients for further investigation.

Ultrafiltration during dialysis

The effect of simultaneous filtration during dialysis is complex and cannot be dealt with in its entirety here.^{10,16,17} The clinician should be aware that the additional urea clearance from ultrafiltration during hemodialysis (Q_f) is small and depends on the extraction ratio (ER). For example, if ER is zero (no solute removal by diffusion), the clearance is simply Q_f . If ER is 100%, ultrafiltration adds nothing to dialyzer clearance because one cannot improve on 100% removal. For the latter case, however, during the entire dialysis, there is a potential effect on solute removal because the water space contracts around the solute mass, which tends to keep the solute concentration higher during dialysis, enhancing removal by diffusion. The net result is a larger removal rate for a given urea reduction ratio (URR; see discussion below) and a lower predialysis concentration when one considers the more global picture of urea mass balance shown in Figure 2. As an extreme example, if the patient gained enough fluid between dialysis procedures, the BUN would not increase, and "dialysis" would consist entirely of ultrafiltration, with $Kt/V_{\text{urea}} = (Q_f \times t)/V_{\text{urea}}$. URR in this example would be zero despite adequate dialysis.

Hemodialysis-induced solute disequilibrium

Closer analysis of urea kinetics during dialysis shows that the simple single-compartment model fails to accurately predict urea concentrations during and after a dialysis treatment. Figure 4 shows that urea concentrations decrease more steeply during hemodialysis than the model predicts and that the postdialysis rebound is not predicted by the model. Both of these deviations from the single-pool model are due to urea disequilibrium.

Disequilibrium results from restrictive movement of a solute among the patient's tissue compartments, causing concentration gradients to develop especially during

rapid solute removal. Sequestration of solutes in remote tissues tends to accentuate the self-limiting nature of intermittent dialysis (see "Limitations of hemodialysis") by further restricting delivery of the solute to the dialyzer.

Solute gradients that result from this multicompartiment phenomenon have two sources:

- Classic diffusion-dependent or membrane-dependent disequilibrium; and
- Blood flow-dependent disequilibrium.

Diffusion-dependent disequilibrium illustrated in Figure 5 is caused by a finite rate of solute transport into the dialyzed compartment, for example, extracellular or blood compartment, from a remote compartment, for example, the intracellular compartment. The more prolonged component of urea rebound shown in Figure 4, lasting from 5 to 60 min after dialysis, is caused by dissipation of the concentration gradients between the dialyzed and the remote compartments that were set up during dialysis.

The early component of rebound is caused by another phenomenon unrelated to diffusion barriers and is

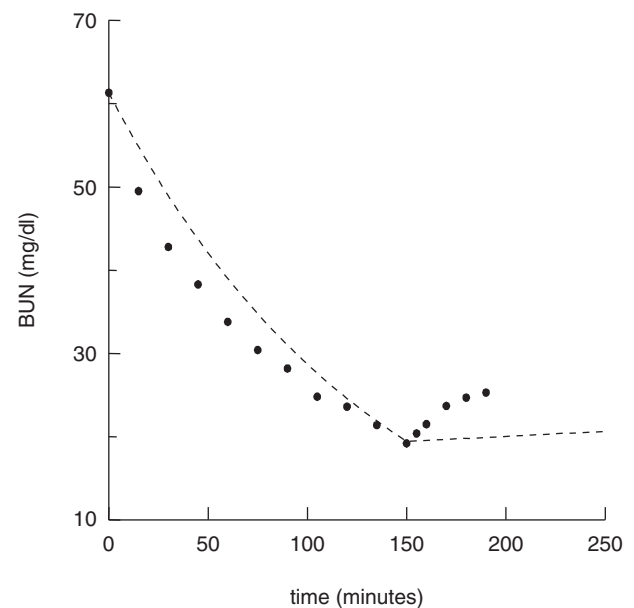


Figure 4 BUN measurements taken every 15 min during a single dialysis (●) show that the single-compartment model of urea mass balance (- - -) diagrammed in Figure 2 overestimates the concentrations during dialysis and fails to predict the rebound postdialysis.

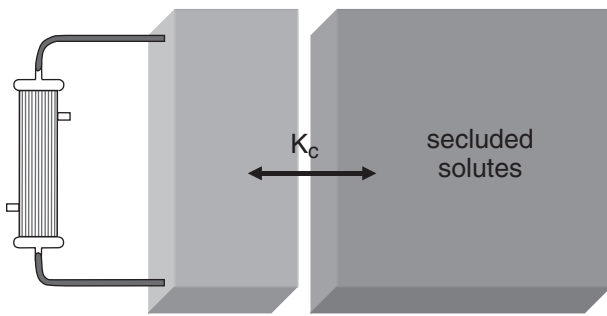


Figure 5 A two-compartment model of solute kinetics during hemodialysis. The essential feature is a resistance to diffusion between the compartments expressed as a finite (low) mass-transfer coefficient (K_c).

predictable when there are disparities in blood flow rates among different tissue compartments.

Flow-related disequilibrium

Flow-dependent disequilibrium causes solute gradients to form within the blood compartment. Figure 6 shows the patient's circulatory system as a series of parallel circuits.¹⁸ The concentration of solute in well-perfused tissues decreases rapidly during dialysis whereas the concentration in poorly perfused compartments remains relatively high. This accounts for the difference in urea concentration that can be demonstrated in blood drawn simultaneously from the opposite arm and the access arm during a dialysis treatment.¹⁸ The round-trip circulation time for the most rapidly flowing pathway, the cardiopulmonary circuit, is typically 10 to 15 s, whereas blood flowing through the slowest pathway may require several minutes to complete the circuit.¹⁹

Timing of the postdialysis blood sample

Figure 7 is a diagram showing an example of different postdialysis BUN levels depending on how and when the blood sample is drawn from the arterial line (line flowing into the dialyzer) at the end and up to 60 min after the end of a hemodialysis. Proposed sampling times are shown as points A through D.

- A The immediate postdialysis BUN in a patient with significant access recirculation.
- B The immediate postdialysis BUN after taking precautions to wash out the recirculated blood from the arterial inflow line. At this point, standard single-

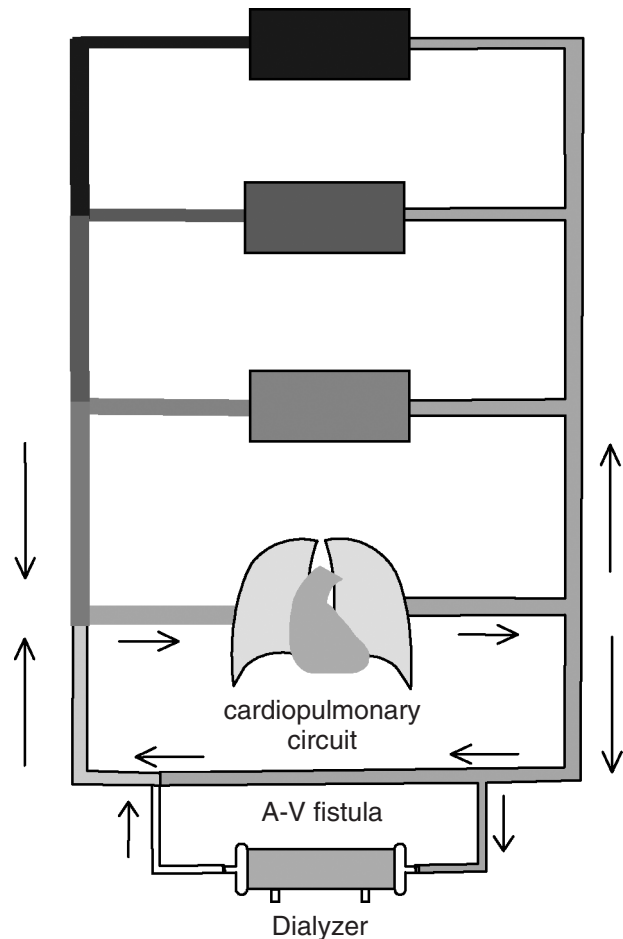


Figure 6 Flow-dependent disequilibrium results from variable flow/tissue mass ratios. Solute delivery from poorly perfused compartments is delayed, setting up gradients that reduce the effectiveness of the dialyzer.

compartment urea modeling gives the most accurate value for the patient's urea volume (V_{urea}).

- C Rebounded BUN 2 min after stopping the blood pump. When dialysis ceases, reequilibration (mixing) of the blood compartment causes a rapid increase in the BUN, beginning as early as 10 s after stopping dialysis. After approximately 2 min the effect of cardiopulmonary recirculation is dissipated but the BUN continues to increase at a less rapid pace owing to flow-dependent and membrane-dependent reequilibration of the blood with remote body compartments.
- D After 60 min, all compartments are equilibrated and the BUN reflects uniform urea concentrations throughout the body. For urea, equilibration is approximately 95% complete at 30 min after dialysis.

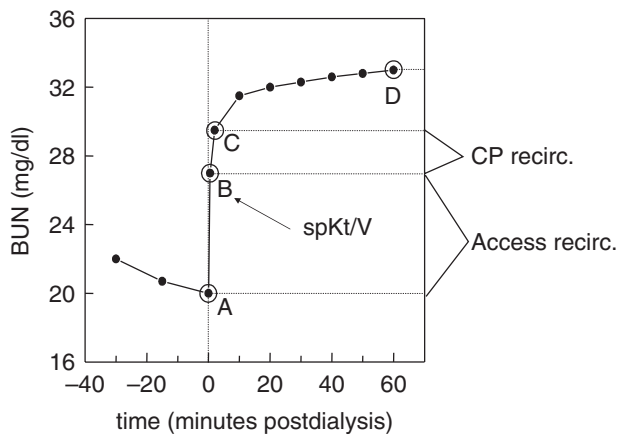


Figure 7 Timing the postdialysis BUN sample. Sampling at point B, taking precautions to avoid errors attributed to access recirculation (Access recirc.) and urea rebound, will ensure accuracy and consistency of Kt/V_{urea} measurements. See text for details. CP recirc. = cardiopulmonary recirculation.

The best point to measure the postdialysis BUN is point B, which is the point on which current dialysis standards are based. When the sample is taken at point B, the resulting K in $spKt/V_{urea}$ matches the dialyzer clearance best because the errors in the single-pool model, shown in Figure 4, tend to cancel one another.¹⁰

How to draw the postdialysis blood sample

The steps for drawing the postdialysis blood sample are as follows:

- Turn off ultrafiltration.
- Slow the blood pump to 100 mL/min for 10 s and then stop the pump.
- Draw blood sample from the arterial (dialyzer inflow) blood port.

eKt/V_{urea} from the equilibrated postdialysis BUN

Because the urea concentration rebounds significantly postdialysis, a more realistic measure of the effectiveness of dialysis is derived from the ratio of the predialysis BUN to the equilibrated postdialysis BUN depicted in Figure 8. Measurement of this concentration, however, is problematic because it requires that the patient wait for

at least 30 min after the treatment to draw the blood sample. Fortunately, Kt/V_{urea} based on the equilibrated postdialysis BUN value can be predicted from relatively simple mathematical equations that relate the equilibrated eKt/V_{urea} to the intensity of dialysis or conversely, to the duration of dialysis.²⁰⁻²²

$$eKt/V_{urea} = spKt/V_{urea} - 0.6(K/V) + 0.03.^{20} \quad (9)$$

$$eKt/V_{urea} = spKt/V_{urea} (t/(t + 35)).^{21} \quad (10)$$

Both Equations 9 and 10 predict that reducing time on dialysis while maintaining the same $spKt/V_{urea}$ will reduce the effective clearance.

Simplified equations for $spKt/V_{urea}$ and PCRn

Because formal urea modeling requires a computer and specialized software, attempts have been made to simplify the calculation of $spKt/V_{urea}$ by fitting empiric equations containing the essential variables found in

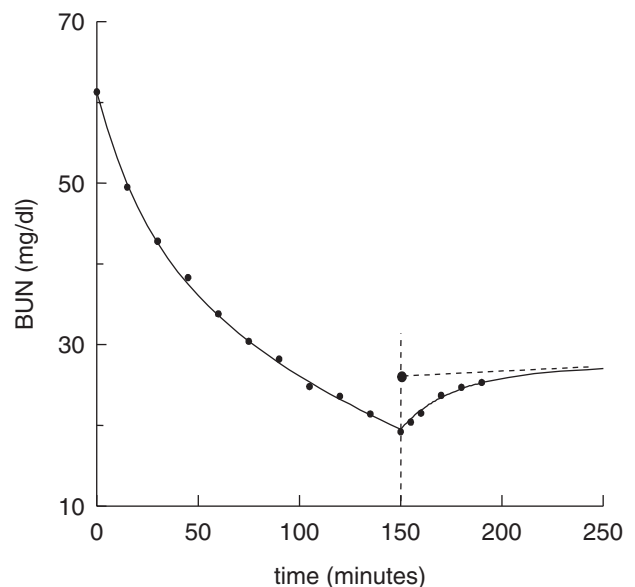


Figure 8 The equilibrated postdialysis BUN can be calculated from an extrapolation of the rebound curve (horizontal dotted line), correcting for urea generation during the rebound period. The resulting BUN is the basis for eKt/V_{urea} , which can be estimated from $spKt/V_{urea}$ using simple equations (see text).

Equation 6. The most widely used equation was devised by Daugirdas in 1993.²⁰

$$\text{spKt}/V_{\text{urea}} = -\ln(R - 0.008t) + (4 - 3.5R)\Delta\text{BW}/\text{BW}, \quad (11)$$

where R is $\text{BUN}_{\text{post}}/\text{BUN}_{\text{pre}}$ and BW is body weight.

Once $\text{spKt}/V_{\text{urea}}$ is determined, PCRn can also be estimated using similar empiric equations based on the predialysis BUN.²³

The urea reduction ratio (URR)

A crude assessment of the effectiveness of dialysis can be obtained by simply noting the magnitude of the decrease in BUN, usually expressed as a fraction or percentage of the predialysis BUN. The relationship between $\text{Kt}/V_{\text{urea}}$ and URR is logarithmic (curvilinear) and depends on the amount of fluid removed during the treatment as noted above (see “Ultrafiltration during dialysis”). As more fluid is removed during dialysis, URR decreases whereas $\text{Kt}/V_{\text{urea}}$ remains constant or actually increases slightly owing to the additional clearance from ultrafiltration. For example, when $\text{Kt}/V_{\text{urea}}$ is at the minimum standard of 1.2 per dialysis, URR is 65% only when fluid removal is between 2 and 4% of body weight. When the weight gained between dialysis procedures is greater, URR is lower and when the weight gain is less, URR is higher, despite constant $\text{Kt}/V_{\text{urea}}$. Although simple to calculate, this measure does not suggest a method for correcting a value that is out of the target range and it provides no measure of PCRn. URR approaches zero in patients with continuous removal, so it cannot be used to assess peritoneal dialysis or normal renal function.

Adding residual native kidney clearance (Kr) to dialyzer clearance (Kd)

Methods for adding continuous Kr_{urea} (Kr) to intermittent Kd_{urea} (Kd) to produce a summed clearance (K) have not been standardized. One approach is to reduce the discontinuous clearance to a continuous equivalent, allowing simple addition. The other is to convert the continuous native kidney clearance to an intermittent equivalent before addition. Because standards have been set for thrice-weekly dialysis, the latter is the approach most commonly used today, but a growing interest in

more frequent dialysis has begun to focus more attention on continuous equivalent clearances (see below).

Transforming Kr to an intermittent equivalent clearance

Two basic approaches have been proposed, one aimed at achieving a continuous BUN equivalent to the mean predialysis BUN²⁴ and the other targeting the mean BUN.²⁵ These similar methods are relatively straightforward and require two steps:

- Model the dialysis using measured predialysis and postdialysis BUN values, including Kr to obtain G_{urea} (G).
- Fix G at this value, eliminate Kr, and repeat the modeling to calculate a new value for Kd that would be required to achieve the same predialysis or mean BUN.

The new Kd represents the effective summation of the two clearances. The argument in favor of the predialysis BUN approach is based on theoretical peak concentration toxicity. Another argument is based on demonstrated solute disequilibrium that causes the mean concentration of other probably more toxic solutes to be much closer to their predialysis concentrations. These two arguments are related, and mathematical predictions generated from each of the theoretical constructs give similar results.²⁶

A simplified approach to adding residual clearance

To add Kr to Kd, one must take into consideration the different durations of their effects, which is usually 3 to 5 hr, thrice weekly for Kd and 168 hr per week for Kr.

$$\text{Kt}/V_{\text{urea}} = (\text{Kd} \cdot \text{Td} + \text{Kr} \cdot \text{Tr})/V_{\text{urea}}, \quad (12)$$

where Td is time on dialysis and Tr is the mean time interval between two dialysis procedures.

Continuous clearances, however, are more efficient than intermittent clearances, especially when fewer treatments are given per week. To account for this improved efficiency while simplifying the calculation and avoiding the extra formal modeling steps listed above, the time factor (Tr) can be altered to inflate the effect of Kr.²⁷ This adjustment can be based either on the predialysis BUN approach or on the mean BUN approach described above. It is an approximation that is absolutely accurate only for the average patient, but the errors are usually negligible, because the additional effect of Kr is small compared to the effect of Kd.

Inflation of Tr to allow adding Kr to Kd (Equation 12) accounting for the enhanced efficiency of Kr

Inflation of Tr is shown in Table 1. Residual urea clearance is highly correlated with patient survival, more so than dialyzer Kt/V_{urea} , so despite the marked inflation based on the predialysis BUN at low frequencies, application of the Tr values in the last column is unlikely to endanger patients from underdialysis.^{28,29}

Measuring more frequent dialysis

- Intermittent dialysis causes a change in solute concentration.
- Intermittent dialysis is punctuated by periods of no dialysis.

Although these differences seem obvious, they account for the markedly higher efficiency of solute removal and solute level control by continuous dialysis. Past obsessions with improving dialysis by maximizing the therapy during treatment ignored the absence of dialysis and unfettered rise in toxin concentration that occurs between treatments. For a 4-hr treatment thrice weekly, no dialysis occurs 93% of the time. There is limited opportunity to control the concentration of a solute that is continually generated independent of dialysis. As an extreme example, it is possible to completely remove all solute during dialysis (extremely high K/V_{urea}) yet be left with relatively high mean levels because of accumulation between treatments. Doubling the extremely high K/V_{urea} in this case would have no effect on toxin concentrations. This misleading nature of Kt/V_{urea} as an index of dialysis adequacy has been addressed by converting it to a continuous equivalent of dialyzer clearance. For continuous dialysis, solute levels in general relate inversely to the clearance, analogous to the inverse relationship between creatinine levels and creatinine clearance in people who

Table 1 Inflation of Tr (allows addition of Kr to Kd using equation 12)

Number of treatments per week	No Inflation	To Mean BUN ¹⁰	To Predialysis BUN ²⁷
2	5040	6500	9500
3	3360	4000	5500
4	2520	2850	3700
5	2016	2200	2700
6	1680	1780	2100
7	1440	1500	1700

do not require dialysis. Complex mathematical expressions have been developed for converting $spKt/V_{urea}$ or eKt/V_{urea} to its continuous equivalent clearance that are beyond the scope of this review.^{24,25,30} However, if formal urea modeling (see above) is available, these calculations are greatly simplified.

Continuous equivalent clearance expressions

Continuous equivalent clearance expressions include

- $EKR = G_{urea}/(\text{time-averaged BUN})$;³¹
- $stdK = G_{urea}/(\text{average predialysis BUN})$;²⁴ and
- $nK = G_{urea}/(\text{mean concentration of a sequestered solute})$.³⁰

All three definitions are based on the assumption that in a steady state of protein balance, the urea removal rate is equal to the urea generation rate (G_{urea}). As noted above, formal urea modeling provides G_{urea} , the time-averaged BUN, and the mean predialysis BUN for these calculations. EKR is the continuous equivalent urea clearance based on the usual definition of clearance as the removal rate/C (see above discussion of clearance).¹⁰ Standard clearance (stdK) is a redefined clearance expressed as the removal rate divided by the mean predialysis BUN.²⁴ For intermittent dialysis, the predialysis BUN is always higher than the mean BUN, so stdK is always lower than EKR. Normalized K (nK) is the continuous equivalent clearance of an easily dialyzed solute that behaves like urea in this respect, but is more tightly sequestered in remote tissue spaces during dialysis (see Figure 5), causing a greater rebound in concentration postdialysis.³² All three continuous clearance equivalents can be expressed as a fractional clearance (e.g., $stdKt/V_{urea}$) usually on a weekly basis. All three expressions approach each other as the frequency of dialysis increases and are identical for continuous dialysis.

Advantages of continuous equivalent clearances

Advantages of continuous equivalent clearances include

- Realistic adjustment for the inefficiency of intermittent dialysis;
- One standard target dose for all patients regardless of frequency and duration;
- Simple addition of Kr to Kd; and

- Comparison of hemodialysis and peritoneal dialysis doses.

Continuous equivalent expressions of the dialysis dose allow simple addition of native kidney clearance to the dialyzer clearance as discussed above. For example, if K_r is 2 mL/min and $\text{stdKt}/V_{\text{urea}}$ provided by the dialysis is 3.2/week in a 40-L patient, then the total weekly $\text{stdKt}/V_{\text{urea}}$ is $2 \text{ mL/min} \times 10,080 \text{ min/week}/40,000 \text{ mL} + 3.2/\text{week} = 3.7/\text{week}$.

Summary: expressions of delivered dose using variants of Kt/V_{urea}

Expressions of delivered dose using variants of Kt/V_{urea} include

- $\text{spKt}/V_{\text{urea}}$, dialyzer clearance;
- $\text{dpKt}/V_{\text{urea}}$, dialyzer clearance (more accurate);
- $\text{eKt}/V_{\text{urea}}$, patient clearance;
- $\text{EKRT}/V_{\text{urea}}$, continuous equivalent clearance based on control of mean urea concentrations;
- $\text{stdKt}/V_{\text{urea}}$, continuous equivalent clearance based on control of peak urea concentrations; and
- $\text{nKt}/V_{\text{urea}}$, continuous equivalent clearance based on control of mean concentrations of a solute that is less diffusible than urea.

Although $\text{spKt}/V_{\text{urea}}$ ignores urea disequilibrium, the resulting two errors nearly cancel one another when dialysis is delivered for 3 to 5 hr thrice weekly. The equilibrated $\text{eKt}/V_{\text{urea}}$ accounts for the improved efficiency of more prolonged dialysis at the same $\text{spKt}/V_{\text{urea}}$. The continuous equivalent expressions of clearance allow addition of continuous native kidney and/or peritoneal urea clearance to intermittent (hemodialysis) urea clearance. Standard Kt/V_{urea} ($\text{stdKt}/V_{\text{urea}}$) and $\text{nKt}/V_{\text{urea}}$ account for the improvement in dialysis efficiency observed for continuous forms of dialysis that exceeds expectations based on mean urea concentrations alone.

Current recommendations for adequate dialysis

Current recommendations for adequate dialysis include:

- For three treatments per week

Target $\text{spKt}/V_{\text{urea}} = 1.3$; minimum = 1.2 per dialysis (K/DOQI standard).³³

Alternatively, target $\text{stdKt}/V_{\text{urea}} = 2.3$; minimum = 2.0 per week.

- For four treatments per week

Multiply $\text{spKt}/V_{\text{urea}}$ by 4 (to convert to weekly $\text{spKt}/V_{\text{urea}}$) and then divide by 3 to get a thrice-weekly equivalent. Target $\text{spKt}/V_{\text{urea}}$, 1.0; minimum, 0.9 per dialysis. This is a conservative approach.

Alternatively use the same weekly $\text{stdKt}/V_{\text{urea}}$ targets listed above for $3\times/\text{week}$ dialysis.

When Kt/V_{urea} is misleading

Four potential sources of error when calculating and interpreting Kt/V_{urea} are as follows:

- Drawing the postdialysis BUN incorrectly. Care must be taken to follow the protocol (see above) to avoid errors attributed to access recirculation, rapid BUN rebound after dialysis, and dilution of the BUN with saline or transfused blood.
- $\text{spKt}/V_{\text{urea}}$ as classically measured using formal urea modeling is defined as a function of dialyzer clearance. Adding the patient's residual clearance to the dialyzer clearance is complicated because one is intermittent and the other is continuous, and they occur at different times. As discussed above, these two clearances cannot simply be summed arithmetically.
- The standards for Kt/V_{urea} are based on three dialysis procedures per week on a Monday, Wednesday, Friday or Tuesday, Thursday, Saturday schedule. When the schedule deviates from this, the standards no longer apply. The most common deviation is twice-weekly dialysis. One cannot simply increase thrice-weekly Kt/V_{urea} by 50% to accommodate dialysis on a twice-weekly basis.
- An increase in urea generation occurs as a result of intradialysis infusions of parenteral nutrition containing relatively large amounts of amino acid. The increased urea generation reduces the decrease in BUN, falsely lowering Kt/V_{urea} when calculated by methods that do not account for the temporary elevation in G .³⁴

In addition, the modeled value for PCRn may be falsely low in a patient with unrecognized residual renal function. In a patient who has lost residual function, failure to delete K_r from the formal modeling equations will cause both a falsely high PCRn and a risk of underdialysis,

potentially endangering the patient. The troubleshooting of urea modeling measurements¹⁰ is shown in Table 2.

Limitations of hemodialysis

Both uremic toxicity and its treatment by dialysis or filtration are concentration-dependent. In other words, the higher the concentration the worse the toxicity, but also the more effective the treatment. One can extrapolate from this line of reasoning that as the concentration is lowered, the patient becomes less toxic but the treatment becomes less effective. One might also imagine that at some point in the treatment, the patient's health is improved but the treatment no longer works. When that point is reached, is the patient completely cured or only partially cured? Furthermore, does the method or technique for delivering dialysis determine when that point is reached?

Recent data obtained from the HEMO Study, a randomized controlled clinical trial of dialysis dose and membrane flux, showed a plateau effect with respect to small-solute clearance, because increasing the clearance above current standards showed no benefit.² The ongoing high mortality rate (17%/year in the HEMO Study), however, suggests that the treatment is incomplete. Exactly how it is incomplete remains a mystery. Many investigators have attempted to capitalize on the original incredible success of dialysis (see above) by applying more dialysis in different ways, prolonging the treatment, increasing the flow rates, increasing the frequency, or even providing continuous treatment akin to

the native kidney. The unexpected and somewhat unexplained success of continuous peritoneal dialysis where urea clearances are as low as one-tenth of that achieved by hemodialysis suggests that the intermittence of today's typical dialysis schedule is the problem. Uncontrolled trials of more frequent hemodialysis including home nocturnal dialysis suggest that much can be gained by increasing the frequency of treatments.

Other possible causes of the high morbidity and mortality rates in hemodialyzed patients include a legacy of comorbidity that each patient brings to the dialysis clinic or possibly a yet undiscovered function of the native kidney that is not reproduced by dialysis.

Despite the high mortality rate, some patients live for many years, more than 30 years in reported cases. These individuals may be exceptional, perhaps adapting to the loss of kidneys in a way that allows prolonged survival, an adaptation that not all patients can muster.

Ongoing concerns

An apparent incomplete treatment effect of infrequent dialysis can be predicted on a theoretical basis by multi-compartment models that account for solute sequestration. The ceiling effect observed in the HEMO Study patients is consistent with this construct but does not exclude other potential causes of the persistent high mortality rate observed in this country, including patients enrolled in the HEMO Study. Other potential causes of this "residual syndrome" include comorbidity associated

Table 2 Troubleshooting urea modeling measurements¹⁰

Problem	Possible causes
Kt/V _{urea} higher than predicted, e.g., > 2.5/dialysis 3×/week	Almost always attributed to drawing the sample from the venous rather than arterial port Dilution of postdialysis blood sample with injected saline or transfused blood
Kt/V _{urea} lower than predicted	Access recirculation Wrong dialyzer or incorrect K ₀ A Undetected early termination of treatment Dialyzer clotting or loss of surface from reuse Reversal of blood/dialysate flow directions Wrong or nonoccluding blood pump segment Inaccurately calibrated blood pump Drawing the predialysis sample after starting the blood pump Intradialysis infusions of parenteral nutrition
PCRn lower than expected	Underestimation or nonrecognition of Kr
PCRn higher than expected	Overestimation or failure to recognize loss of Kr

with prolonged renal failure preceding the initiation of dialysis, accumulation of poorly dialyzable solutes, a yet undiscovered function of the native kidney, or an adverse effect of dialysis.

Current recommendations

- Continue to use urea (small-solute) clearance as the primary index of dialysis dosing and adequacy.
- Follow K/DOQI guidelines for $\text{spKt/V}_{\text{urea}}$ in patients dialyzed three times weekly (target, 1.3 vol; minimum, 1.2 vol per dialysis).
- Include residual clearance in the measure of delivered dose.
- Compare delivered with prescribed dose. If they differ by more than 15%, troubleshoot.
- Consider increasing the dose if health and nutrition show signs of failing, especially in smaller patients and in women.
- For more frequent dialysis, use standard $\text{Kt/V}_{\text{urea}}$. Set minimum to 2.0 vol/week.
- Be alert to new treatments that may minimize or eliminate the residual syndrome.

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