
CORRESPONDENCE

EKR_c Versus stdKt/V: What's the Difference? What's the Meaning?

Editors' note

The article by Piccoli *et al.*, "Daily Dialysis and Flexible Schedules: How to Assess Kt/V and EKR_c?" (*Hemodial Int* 2001; 5:13–18) has prompted an interesting discussion among experts on dialysis kinetics. Piccoli *et al.* reported a study on measurements of dialysis dose in daily (six times weekly) home hemodialysis with a flexible schedule, where changes in dialysis duration and distribution during the week were permitted to give patients maximum freedom in scheduling, but maintain efficiency of the dialysis. Because there were no established criteria for adequate dose of dialysis performed more frequently than three times weekly, the authors selected the Casino–Lopez model [corrected equivalent renal clearance (EKR_c)] of comparison between various frequencies of weekly hemodialysis sessions [1]. Using this model, they determined that, to reliably assess the efficiency of dialysis with a flexible schedule, the average clearance of three or more sessions is needed to determine EKR_c.

The Editors asked Dr. Frank A. Gotch to write an accompanying commentary on the methods of comparing efficiencies of various dialysis frequencies. In his commentary [2], Dr. Gotch argued that his concept of stdKt/V is better than the Casino–Lopez model for this purpose.

This commentary prompted Dr. Gerald Glancey to send a letter to the Editor, which was in turn sent to Dr. Gotch for reply. A discussion via the Internet between Drs. Glancey and Gotch ensued. They both agreed that Eq. 6 (in Ref. [2]) is incorrect and only an approximation, but otherwise seemed to stick to their guns. Their correspondence was sent to Drs. Depner and Daugirdas, experts in kinetic modeling, for further discussion of this interesting problem. We have decided to publish the entire correspondence, as it is very interesting from the theoretical point of view.

To set the stage for further discussions, let us review the definitions:

According to Gotch, $\text{stdK} = G / m\text{Co}$, where stdK is continuous standard clearance, G is urea nitrogen generation rate, and mCo is the mean pre-dialysis urea nitrogen concentration.

$\text{StdKt/V} = [\text{stdK} (7)(1440) / N] / V$, where stdKt/V is a standardized dose of dialysis, 7 and 1400 stand for the number of days per week and number of minutes per day, N is the number of dialyses per week, and V is urea distri-

bution volume, which is roughly equivalent to total body water.

$\text{EKR} = G / \text{TAC}$, where EKR is equivalent renal clearance, G is urea nitrogen generation rate, and TAC is time-averaged concentration of urea nitrogen.

$\text{EKR}_c \text{t/V} = [\text{EKR} (7)(1440) / N] / 40$, where EKR_c is corrected EKR and 40 is the standard volume normalization parameter, assumed to be 40 L.

In his commentary, Gotch presented the following relationship between G, TAC, and TAK, where TAK is time-averaged clearance during dialysis:

$$G = \text{TAK} (\text{TAC}) \text{ [Eq. (6) in Gotch's commentary].}$$

Thus $\text{TAK} = G / \text{TAC}$ [Eq. (7) in Gotch's commentary], hence $\text{EKR} = \text{TAK}$.

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Dr. Glancey's letter to the Editor

Sir:

Professor Gotch's Commentary in *Hemodial Int* (2001, Vol. 5, pages 102–105) is incorrect regarding its analysis of the "equivalent renal clearance" (EKR) model of dialysis adequacy.

The error lies in Eq. (6) in the text where G is equated to TAK(TAC), where TAK is the time-averaged sum of all the first-order clearances (sum of Kt) / T, and TAC is the mean urea concentration averaged over the whole dialysis cycle. TAC should be replaced by the mean urea concentration during dialysis only. Having made the above correction it is obvious that, whereas $\text{EKR} = G / \text{TAC}$ (by definition), TAK does not, and therefore, EKR does not equal TAK, as Prof. Gotch asserts. In fact, EKR parallels stdK (the "standardized" clearance), except that, as $\text{stdK} = G / (\text{mean Co})$, whereas $\text{EKR} = G / (\text{TAC})$, EKR would be a little less than twice stdK in most instances. It is surely just a matter of personal preference

whether one uses EKR or stdK, although I would tend toward the former.

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Dr. Gotch's reply

Sir:

Dr. Glancey argues that the expression

$$G = \text{TAK}(\text{TAC}), \tag{1}$$

where TAK is total intermittent clearance averaged over a week, and TAC is time-averaged BUN over a week, is incorrect and should be

$$G = \text{TAK}(\text{TAC}_{\text{during dialysis}}). \tag{2}$$

Dr. Glancey is correct that Eq. (1) is an approximation of Eq. (2), and this should have been more clearly stated in the commentary. However, he seriously misinterprets the significance of this approximation. The $\text{TAC}_{\text{during dialysis}}$ will be a little lower than the overall TAC averaged over the total cycle, since $\text{TAC}_{\text{during dialysis}}$ is approximately equal to the log mean of pre and post BUN, while TAC over the entire cycle is the sum of the short interval log mean and the longer interval arithmetic mean.

However, the effect of this difference is trivial in the usual range of dialysis therapy, as illustrated in Fig. 1. The curves in Fig. 1 were derived from iteration to steady state of the double-pool urea model for three times weekly hemodialysis, with equilibrated Kt/V (eKt/V) varied over the range on the abscissa. At each level of eKt/V, the model was solved for the BUN profile with known generation rate, and stdKt/V, EKrt/V, and TAKt/V were calculated. An eKt/V of 1.05 (corresponding to single-pool Kt/V of 1.2 to 1.3, depending on treatment time) is depicted as adequate hemodialysis. Note that TAKt/V increases linearly, as would be expected, and that EKrt/V is virtually identical to TAKt/V for eKt/V ≤ 1.05. At the eKt/V of 1.45 (a very high dose of dialysis), the ratio EKrt/V / TAKt/V is 0.88. Thus, it is clear that the approximation in Eq. (1) above is not misleading in the clinically relevant domain of therapy. It is also important to note that TAK is not a modeled dose parameter and was used only to approximately illustrate the meaning of EKR.

Dr. Glancey also states that the EKR is simply "a little less than twice the stdK in most instances" and that "it is surely a matter of personal preference whether one uses EKR or stdK." This is refuted in Fig. 1, where the most important observation is that stdKt/V predicts the correct dose for ad-

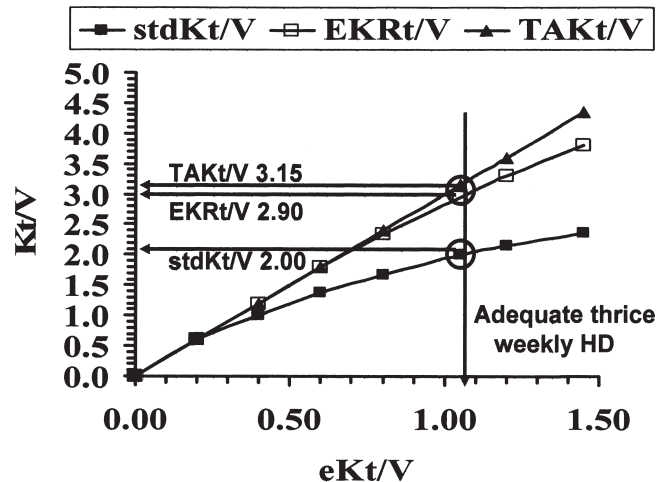


Figure 1 The stdKt/V model correctly predicts that a weekly Kt/V of 2.0 in CAPD provides therapy equivalent to adequate three times weekly hemodialysis. In contrast, the EKrt/V model predicts a weekly Kt/V of 2.9 would be required for adequate CAPD. (Modified from Gotch F. Modeling the dose of home dialysis. Home Hemodial Int. 1999; 3:37-40.)

equate CAPD (a weekly Kt/V 2.0), while the EKrt/V predicts adequate CAPD would require a weekly Kt/V of 2.9, which is 50% higher (not twice as high) than the dose clinically considered adequate. The stdKt/V correctly normalizes the dose in two benchmark dialysis therapies (continuous ambulatory peritoneal dialysis and intermittent three times weekly hemodialysis), but the EKrt/V does not. Clearly, stdKt/V and EKrt/V cannot be considered equivalent dose normalization parameters, as suggested by Dr. Glancey.

StdKt/V and EKrt/V are fundamentally different parameters conceptually. The standard clearance concept derives from the assumption that the efficiency and effectiveness of dialysis are directly proportional to the rate of solute removal, which is always maximal at the beginning of each treatment and progressively falls as BUN and other solute concentrations fall during dialysis. Thus, it can be hypothesized that a continuous clearance with efficiency equivalent to that at the beginning of each intermittent treatment would be as effective as the summed intermittent clearances with any treatment schedule. This equivalent clearance is the stdK and is defined as

$$\text{stdK} = G / \text{mean pre-dialysis BUN}. \tag{3}$$

StdK is a continuous effective clearance reflecting the maximal average rate of solute removal at the beginning of each dialysis. In contrast, EKR is defined as

$$\text{EKR} = G / \text{TAC}. \tag{4}$$

EKR is a rigorous mathematical analogue of a continuous clearance, defined as generation divided by the time-aver-

aged concentration, but it contains the implicit assumption that clearance at the end of dialysis, when solute concentrations are very low, is just as effective therapeutically as clearance at the beginning of dialysis. This does not intuitively make sense with first-order processes, and clearly fails to predict clinically equivalent doses in CAPD and three times weekly hemodialysis.

I thank Dr. Glancey for his comments and hope this may help to clarify the differences between the two models.

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Dr. Glancey's rebuttal

Sir:

I would just like to pass comment on Prof. Gotch's reply to my earlier email regarding the above.

Basically, Prof. Gotch does seem to admit to the mathematical error that invalidates many of the very specific assertions contained in his original commentary. Unfortunately, his reply still seeks to justify the basic tenets of his original commentary.

Rather than go through the whole reply in critical detail, I should just like to restate some facts about EKR and stdK in order to clarify the situation.

EKR and stdK are both just mathematical concepts that can be ascribed specific values when derived from a particular set of dialysis parameters, which in this case are in relation to a three times weekly hemodialysis regime in a hypothetical patient presumed to be in equilibrium.

In the case of stdK, the value derived represents the equivalent continuous clearance that would lead to the same patient having a constant urea concentration equal to the mean 3× weekly pre-hemodialysis urea concentration. The value derived is essentially arbitrary and has no direct relevance whatsoever in determining what an equivalent "adequate" weekly CAPD Kt/V should be. [That the two weekly clearance figures turn out to be very similar is just a reflection of the fact that history, experience, and practical/physiological restraints on the size of CAPD prescriptions have meant that, in practice, the total weekly urea reduction ratio (or clearance) on CAPD tends to be very similar to the aggregate weekly urea reduction ratio on 3× weekly "adequate" hemodialysis, so that the urea concentration on CAPD must match the mean pre-hemodialysis urea concentration very closely. Given that, it is obvious that calculated stdKt/V for adequate 3× weekly hemodialysis and adequate CAPD Kt/V are going to be the same number, *i.e.*, around 2.]

In the case of EKR, the value derived represents the equivalent continuous clearance that would lead to the same patient having a constant urea concentration equal to the time-

averaged urea concentration over the whole 3× weekly hemodialysis cycle.

Both EKR and stdK are derived from essentially the same data set, and both are sensitive to the greater effect that daily hemodialysis has on plasma urea concentration compared to increasing 3× weekly Kt/V. My preference for EKR is based purely on the fact that it derives from a more balanced (*i.e.*, the time-averaged mean) assessment of urea concentration and, therefore, the uremic state of the hypothetical patient throughout the dialysis cycle; whereas, stdK relates only to the peak concentrations, that is, it is far from representative of the patient's overall state of uremia.

A suggestion that I think would simplify matters is perhaps the renal community could adopt, not EKR, but weekly EKRt/V as a measure of dialysis efficiency. Its calculation is potentially very easy and could be derived without significant error by means of the following formula: weekly EKRt/V = (rate of rise per hour of urea concentration in the interdialytic interval) times (168 hours) divided by (TAC of urea). Both the rate of rise of urea concentration and the TAC can be derived without significant error solely from a suitably equilibrated (*i.e.*, timed) post-dialysis and pre-dialysis blood urea estimation.

Gerald R. Glancey, MA, MD, MRCP

Dr. Gotch's response

Sir:

I am afraid that Dr. Glancey and I have irreconcilable differences regarding stdKt/V and EKRt/V. I do want to make a couple of final comments regarding Dr. Glancey's new qualitative arguments.

He continues to state that there was a major mathematical error that invalidates the "basic tenets" of my commentary. I will state again, Dr. Glancey is correct: TAK should be related to $TAC_{\text{during dialysis}}$ rather than TAC over the whole cycle. However, I calculated and showed that the error of this approximation is trivial over the usual clinical range of therapy. But more importantly, TAK was not presented as a dose modeling parameter, that is, a "basic tenet," and has no direct bearing on the validity and interpretation of the two modeled parameters, EKRt/V and stdKt/V.

It is very strange logic to argue that the reason stdKt/V predicts adequate therapy in CAPD and three times weekly hemodialysis is simply a historical accident. Popovich hypothesized that a continuous clearance adequate to maintain BUN at the pre-dialysis level in hemodialysis would provide equivalent therapy. If in fact he had been wrong, and minimum therapy 50% higher, as predicted by the EKRt/V model, were required for adequate CAPD, this fledgling therapy would have promptly perished because of uncontrolled uremia. Instead, it flourished and became the mainstay of uremia therapy in the U.K. Dr. Glancey may not remember the

many criticisms of CAPD in the early days: it “provided only about 2/3 as much clearance as intermittent hemodialysis.” These arguments were eventually refuted only by clinical success of the therapy.

The argument that TAC provides a “more balanced” assessment of urea concentration over the treatment cycle is an accurate, appropriate, mathematical statement, but a leap of faith is required to ascribe clinical meaning to it. In view of the success of CAPD as discussed above, it is more rational to view TAC as a manifestation of the inherent inefficiency of intermittent dialysis, and the price one pays with respect to efficiency in intermittent therapy, rather than as a clinical virtue.

Frank Gotch, MD

Dr. Depner's comments

Sir:

The holy grail of modeling more frequent dialysis is a universal dosing parameter that could be used to compare and contrast renal replacement effectiveness among intermittent treatments with different treatment times and schedules. This universal clearance term would also allow a comparison with continuous dialysis, which is the ultimate high-frequency dialysis, and with native kidney function, which is often significant and occurs simultaneously with intermittent dialysis in the same patient. Expression of the universal parameter as a clearance is reasonable because the most important goal of renal replacement and native kidney function is removal of toxic solutes, a process best expressed as a clearance.

Referring to the data supplied by Piccoli in the same issue (*Hemodial Int* 2001; 5:13–18), Frank Gotch attempts to further define his “standard Kt/V” (stdKt/V), published previously [1], contrasting it with EKRt/V as previously defined by Casino [2] and used by Piccoli. In so doing, however, he introduced a conceptual error. Gerald Glancey correctly points out, as acknowledged by Gotch, that his Eq. (7) is an approximation of Eq. (4) because TAC is defined differently in each. For Eq. (7), TAC is closer to the log mean urea nitrogen concentration during dialysis, whereas, for Eq. (3), TAC is the true mean urea nitrogen concentration averaged over a week [3]. A week is chosen here because dialysis schedules have weekly symmetry, that is, they repeat themselves on a weekly basis. Gotch shows the corrected clearance in a new graph (Fig. 1) but he also shows that the difference is relatively small and the resulting error is insignificant because the log mean concentration is only slightly lower than the mean concentration between dialyses.

However, this difference in effective clearance is responsible for the inefficiency of intermittent dialysis [3]. Since the concentration falls logarithmically during dialysis, the mean concentration, which is the driving force for dialysis,

falls below the arithmetic mean, diminishing the effective patient clearance despite constant dialyzer clearance [3,4]. For an ideal solute with no disequilibrium during dialysis, the difference is small, but for urea, and especially for other solutes that move more slowly out of the patient during dialysis, the difference is more significant [3,4].

All these parameters [EKRt/V, spKt/V (single-pool Kt/V), eKt/V, and standard clearance] are equal to each other in patients treated with continuous hemodialysis, continuous peritoneal dialysis, continuous hemofiltration, and for (continuous) native kidney function. As noted above, the goal of this exercise is to produce an “equivalent” dialysis clearance that can simply be added to and compared with continuous clearance. Equivalency is defined in terms of equivalent outcomes (quality of life, morbidity, and mortality). Simple addition is most beneficial in patients with significant residual renal function where continuous and intermittent clearances occur simultaneously. Current methods for adding the two clearances require complex approximations.

Glancey suggests that either EKR or stdKt/V can be used to quantify dialysis and states that he prefers EKR. The reason for this preference is not clear to me, since the two numbers are quite different for anything but continuous dialysis, and in view of the above goal to develop an equivalent dialysis dose. For example, in a patient receiving three treatments per week with a minimally adequate spKt/V of 1.2 volumes per dialysis, stdKt/V would be 2.0 volumes per week, whereas EKR would be 2.9 per week. Since minimally adequate continuous dialysis also requires a Kt/V of 2.0 volumes per week, the standard clearance expression appears to have achieved the goal of allowing comparison among dialysis schedules, whereas EKR would require a different standard for each schedule and could not be used to compare patients treated at different frequencies.

It should also be noted that the rise in urea concentration between dialyses is not linear for most patients who gain fluid between dialyses and/or have native kidney clearance. Using the equilibrated post- to pre-dialysis urea concentration as suggested by Glancey would underestimate true EKR in these patients.

That stdKt/V appears to predict outcome despite the need to redefine clearance and its awkward reliance on pre-dialysis concentrations — which do not represent the balance of urea exposure, as pointed out by Glancey — is probably a reflection of the inadequacy of urea as a marker of uremic toxicity [5]. As noted above, the difference between the true time-averaged concentration and the log mean concentration during dialysis is accentuated for solutes that move more slowly than urea within the patient, yet are cleared efficiently by the dialyzer. Many small to medium molecular weight solutes found in hemodialysate fit this description. A model based on solute disequilibrium has recently been shown to predict equivalent single-pool urea clearances that are similar to those predicted by the Gotch standard clearance model [6]. This suggests that use of the average pre-dialysis urea nitrogen

concentration in the expression of stdKt/V is indeed fortuitous and may have little meaning in terms of the physiologic toxicity of uremia.

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Dr. Daugirdas' comments

Sir:

Basically, I agree with Dr. Gotch. The time-averaged urea concentration in the Casino–Lopez approach [1] is clearly meant to be the weekly time-averaged concentration and not the intradialytic time-averaged urea. Use of the EKRT/V proposed by Glancey does not solve the problem of inequality between continuous clearance measures of hemodialysis (HD) and peritoneal dialysis (PD). I explain below.

The concept of EKR as described by Casino and Lopez was described as an analogy to creatinine clearance (CCr). Creatinine clearance is commonly measured as UV/P , where UV is the urine concentration of creatinine \times urinary flow rate (to give a creatinine generation rate; let us call it g_{Cr}) and P is the plasma creatinine concentration. Then, if $\text{CCr} = g_{\text{Cr}} / P$, then $\text{EKR} = g_{\text{urea}} / P$.

Both urea generation rate (g) and P, as TAC urea, where this is the average urea concentration per week, can be determined by standard urea kinetic modeling (UKM) programs. If a single-pool program is used, g will be overestimated and TAC will be underestimated, causing a marked overestimation of the EKR.

The Casino–Lopez nomogram relies on knowing the treatment Kt/V and dialysis frequency, and yields values for EKR. It is useful because the calculations are not trivial. Yet, it is not optimal, since it does not account for volume removal and because it was based on a single-pool analysis. The multi-

compartment error can be mostly corrected by using the nomogram with an equilibrated Kt/V value instead of the standard single-pool value (spKt/V). Using the Casino–Lopez nomogram, and assuming a rebound of about 0.20 Kt/V units, one can assume that a typical HD schedule of three times per week will give a spKt/V of 1.2 and an equilibrated Kt/V (eKt/V) value of 1.0. If one inputs a treatment Kt/V of 1.0 and three treatments per week into the nomogram, the predicted g/TAC , or EKR, will be about 11 mL/minute. As there are 10,080 minutes in one week, the weekly EKR is about $11 \times 10,080$, or about 111 L/week. If we divide this by a typical urea distribution volume (V) of 35 L, we get a weekly Kt/V of about 111/35, or 3.2.

The problem is, if minimally adequate HD [urea reduction ratio (URR) 65%, $\text{spKt/V} = 1.2$, 3 \times /week] translates into a weekly Kt/V of 3.2, why is the adequacy standard for another form of dialysis, namely CAPD, only about 2.0 – 2.2? This is about 1/3 less. So, based on urea removal alone, one seems to require 1/3 more equivalent urea clearance on HD. The question is, Why is this so?

Following up on Keshaviah's peak concentration hypothesis [2], Gotch modified the Casino–Lopez idea by dividing g not by TAC, but by the mean pre-dialysis BUN [3]. In a 3 \times /week schedule, the mean pre-dialysis BUN is about 1/3 higher than TAC, and when this adjustment is made, the Gotch EKR, or so called "standard Kt/V " (stdKt/V) for a typical 3 \times /week HD prescription ($\text{spKt/V} 1.2$, $\text{eKt/V} 1.0$, URR 65%) gives a value of about 1/3 less than the Casino–Lopez EKR, or about 7 mL/min. When the clearance is multiplied by 10,080, we get 70 L instead of 11 L, and when we divide by V, the weekly "standard" Kt/V becomes about 2.0, very similar to that obtained with PD.

The question now becomes, true, we get agreement between HD and PD when dividing g by the mean pre-dialysis BUN level instead of by TAC, but is this physiology or a happy numerological accident? Urea is not toxic *per se*, so why should control of peak concentrations of a relatively non-toxic substance mean anything? Presumably, urea is a surrogate for a more toxic solute, X, having similar molecular weight, Dr. Gotch would respond, and one must concede this point.

Depner has proposed an alternative explanation [4]. Prior to applying the Casino–Lopez nomogram at the outset of this discussion, we down-regulated the $\text{spKt/V}_{\text{urea}}$ of 1.2 to 1.0 because of urea rebound. Urea actually equilibrates very rapidly among body compartments and crosses most cell membranes readily. Depner suggested the following: Consider toxic solute Y, similar in weight to urea, perhaps a bit heavier, but with a much larger degree of sequestration during dialysis. Post-dialysis rebound of solute Y would be much greater than the 15% – 20% commonly seen for urea. If we set the inter-compartment transfer resistance of solute Y to give about a 50% post-dialysis rebound, then eKt/V for solute Y would be reduced by another 30%. This would increase TAC for solute Y by about 30% (let us not quibble about the numbers

here), and EKR_{Depner} would be lowered by a third, resulting in an adequacy measure of HD that would be similar to that for PD. So, we can achieve the same numerical adjustment to EKR without invoking the idea of peak concentrations of solutes being important.

To complicate matters a bit further, Keshaviah *et al.* [5] have recently resurrected the peak concentration hypothesis and used it to adjust HD dosage. They propose dividing g by the single highest pre-dialysis BUN instead of the average of the pre-dialysis BUN peaks. For this reason, $EKR_{\text{Keshaviah}}$ will be about 50% of that computed by Casino and Lopez with a 3 \times /week schedule — the adjustment will be even more severe with 2 \times /week therapy, but will approach the Gotch mean pre-dialysis BUN adjustment with 6 \times /week dialysis.

Of the Gotch and the Depner adjustments, which is more appropriate? Who knows. You decide. Why bother with this sort of mathematical discussion at all, one might ask?

There is one important practical application. At this point, with good outcomes data available only for 3 \times /week HD schedules, many centers are struggling with deciding what should be the dose of dialysis for short 6 \times /weekly or 4 \times /weekly or 2 \times /weekly schedules. For a 2 \times /week schedule, if one uses the Gotch approach, namely $g / (\text{mean pre-dialysis BUN})$, one will prescribe more dialysis for a 2 \times /week schedule than when using g / TAC . For a 6 \times /week schedule, the Gotch approach will require a lower daily dose of dialysis. Happily, whether one uses the Gotch or the Depner approach to make the adjustment, the adjustments will be similar, although not identical.

Finally, just to throw a monkey wrench into the HD–PD redux, we know that removal of protein-bound toxins is much greater with PD than with HD. Also, volume control may be important to survival, and this will differ between HD and PD and among the various dialysis schedules, independently of solute removal.

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Editors' comments

The Editors do not believe that there are ultimate criteria of dialysis adequacy at present. The criteria currently accepted by K/DOQI are based mostly on opinion, not on solid facts, and they apply to a three times weekly schedule. The adequacy criteria for more frequent dialysis have not been established, and it is unlikely that a single value of urea clearance will be used in the future. As pointed out in the letters from Depner and Daugirdas, there is more to dialysis than small molecule removal. More frequent dialysis improves removal of substances sequestered in compartment(s) from which they diffuse slowly to the plasma [1,2]. More frequent dialysis decreases fluctuations (unphysiology) of multiple substances and fluid volumes. These fluctuations may have a markedly higher influence on improved results with more frequent dialysis than the clearances of small molecules.

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