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# The current place of urea kinetic modelling with respect to different dialysis modalities

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## Introduction

The range of dialysis treatment schedules is rapidly increasing, with renewed interest in daily haemodialysis (HD), continuous ambulatory peritoneal dialysis (CAPD), automated peritoneal dialysis (APD), APD combined with CAPD, and HD combined with CAPD. A scale has not been developed previously for uniform measurement and comparison of the dialysis doses provided by this broad range of therapies. The purpose of this communication is to report a model which can be used uniformly to measure and thus explicitly compare the doses of dialysis provided by any combination of intermittent and continuous dialysis treatments. In the development which follows, these therapies will be analysed with respect to low molecular weight solute clearance using urea as a generic molecule, and the dialysis doses quantitatively compared with a normal renal clearance reference standard.

## A renal reference standard

In studies of clinical outcome in chronic renal failure, the level of residual renal function is often considered to be defined by the glomerular filtration rate (GFR) [1]. The index of a modern textbook of nephrology usually does not even include the term urea clearance (Kr) which was discarded long ago by renal physiologists as a measure of renal function because of its strong dependence on urine flow rate due to backdiffusion of urea in the tubules.

In sharp contrast, the contribution of residual renal function to renal replacement therapy for end-stage renal disease (ESRD) by HD or PD is usually defined by the renal urea clearance, which is considered to be additive to dialyser or peritoneal clearance provided in dialysis therapy [2]. In keeping with this view of renal function relative to dialysis therapy, it would seem reasonable to define the renal reference standard by renal urea clearance. To the extent that uraemic toxicity is due to accumulation of low molecular weight toxins which are amenable to generic modelling with urea, it is rational to assume backdiffusion of such toxic solutes along the nephron similar to that of urea [3], and hence reasonable to choose Kr as the renal function reference standard for assessing the dose of dialysis.

It is necessary to go back some 50 years to find the major studies of renal urea clearance. The dependence of Kr on urine flow rate (Qu) was modelled by Dole in 1943 [4] as a function of GFR, tubular area, permeability to urea and urine flow rate. These relationships were studied in humans by Chassis *et al.* [5]. The theoretical Dole equation constants were fit to human data of Chassis *et al.* by Homer Smith [6], resulting in

$$\mathrm{Kr} = 0.57(\mathrm{GFR}) * \exp[-0.36/\mathrm{Qu}] \qquad (1)$$

At an average urine flow rate of 1.5 ml/min and a GFR of 100 ml/min, the normal urea clearance calculated from Equation 1 is 45 ml/min. It is proposed that this value, normalized to body water (V) of 35 l, should serve as the normalized renal function reference standard for assessment of the dose of dialysis relative to normal renal function. The continuous peritoneal clearance (Kp) in CAPD is an exact analogue with respect to time of continuous Kr. The CAPD dose conventionally is expressed as Kpt/V, where Kpt is either total daily or weekly peritoneal urea clearance normalized to V. Similar units would seem appropriate for expressing the normal *reference* level of renal urea clearance, ref(Krt/V). Thus ref(Krt/V) can be defined as 0.045*1440/35 = 1.85 l of renal urea clearance per litre of body water daily, or 12.96 weekly. Some perspective on this reference standard is obtained by comparing it with the currently recommended dose in CAPD, a daily Kpt/V of 0.29, or 2.0 weekly, which constitutes ~15% of the normal renal ref(Krt/V) proposed here. In the following model development, the dose provided by any combination of intermittent and continuous therapy will be expressed as standard Kt/V [std(Kt/V)], with daily or weekly units as above, and as a percentage of the normal renal reference standard. In this way, a uniform dose parameter can be applied to any combination of therapy modalities.

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## The conundrum of intermittent *vs* continuous clearance

The basic rationale of dialysis therapy for ESRD is that the uraemic syndrome is due to accumulation of toxic solutes which have concentration-dependent uraemic toxicity which can be controlled by dialysis. Toxic solute removal by dialysis and the human kidney are directly proportional to concentration, so we can write the following general mass balance expression

$$V(dC/dt) = G - K^{*}C \qquad (2)$$

where V is solute distribution volume, G is generation rate and K is clearance. In steady state, such as chronic renal failure or CAPD when $V(dC/dt) = 0$, Equation 2 reduces to

$$0 = G - (Kr + Kp)C \qquad (3)$$

or

$$G = (Kr + Kp)C \qquad (4)$$

Equation 4 describes urea kinetics only with normal renal function, chronic renal failure without dialysis or in CAPD. The relationship of solute concentration to clearance in steady state is demonstrated when Equation 4 is rearranged to give

$$C = G/(Kr + Kp) \qquad (5)$$

Equation 5 demonstrates that C is a precise function of $1/(Kr + Kp)$, which results in the well-known parabolic relationship of C to Kr with vertical and horizontal asymptotes at low and high levels of Kr. This general curve varies for individual patients only as a function of G.

The constant concentrations characterizing the steady-state relationships between C, K and G with continuous clearance no longer hold when intermittent clearance is provided with classical HD therapy. In this case, a saw-tooth profile results, with peak pre-dialysis (Co) and the trough post-dialysis (Ct) concentrations before and after each dialysis separated by gradual concentration build up between treatments, as shown by the profiles in Figure 1. Profile 1 represents pure intermittent HD (IHD) or APD. Profile 2 represents pure continuous clearance as in chronic renal failure or CAPD. Profile 3 represents IHD or APD combined with continuous Kr or Kp between the intermittent treatments.

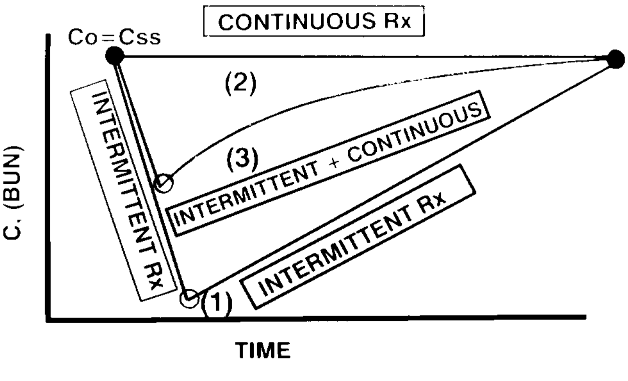

**Fig. 1.** The three basic concentration profiles in dialysis therapy. (1) Intermittent dialysis; (2) continuous dialysis and (3) combined intermittent plus continuous dialysis.

The time-averaged concentration (TAC) with profiles 1 and 3 is substantially lower than the steady-state concentrations shown equal to the pre-dialysis concentration in profile 2, typical with CAPD. The lower TAC in HD compared with steady-state C in CAPD confers no known clinical advantage, since clinical outcome is not related to blood urea nitrogen (BUN) [2], and would seem best interpreted as an inevitable consequence of the high levels of clearance required for intermittent therapy. In typical thrice weekly HD with Kr = 0 as in profile 1, all solute generated between each HD must be removed in only ~5% of the time interval. Consequently, there is a marked reduction in C during each dialysis, which greatly reduces the solute removal rate relative to clearance so that the total clearance provided per week is ~50% greater than in CAPD with continuous clearance and steady-state concentration (Css) equal to pre-dialysis Co. In the model development which follows, the calculated dose [std(Kt/V)] will represent the continuous clearance required for Css = Co as shown in Figure 1, and no advantages will be inferred to result from the lower TACs resulting with intermittent therapy.

## The standard Kt/V model

The kinetic descriptions of intermittent and continuous dialysis which follow contain the assumptions of equally spaced dialyses and constant V. Since ultrafiltration contributes negligibly to low molecular weight solute removal, the assumption of constant V will not cause significant error in calculating std(Kt/V). However, the variable volume model [2] would be required for analysis of *delivered* intermittent dialysis doses in order to estimate the urea distribution volume, V, accurately. The assumption of equal spacing simply provides an estimate of the average peak concentration.

Although the inputs include single-pool Kt/V (spKt/V), correction to equilibrated Kt/V (eKt/V) is made in all instances as a function of the rate of dialysis relative to V [7]. Further, in the case of daily HD and combined therapies, the spKt/V prescribed for each HD may be relatively low, i.e. $<1.1$, which may result in spuriously low calculated V [2,8] which would require an appropriate volume correction algorithm [8] in clinical use.

Equation 2 can now be written in a general form applicable to both intermittent and continuous therapies in accordance with

$$V(dC/dt) = G - (Kd + Kp + Kr)C \qquad (6)$$

Intermittent therapies comprise either intermittent IHD or APD. Solution of Equation 6 for a decrease in BUN over each intermittent therapy session is

$$\mathrm{Ct} = \mathrm{Co}\ \exp[-(\mathrm{Kd\ or\ Kp} + \mathrm{Kr})t/\mathrm{V}] + [\mathrm{G}/(\mathrm{Kd\ or\ Kp} + \mathrm{Kr})] \times [1 - \exp[-(\mathrm{Kd\ or\ Kp} + \mathrm{Kr})t/\mathrm{V}]] \tag{7}$$

where Co is pre-dialysis BUN, Ct is post-dialysis BUN, Kd, Kp and Kr are dialyser, peritoneal and renal urea clearances respectively, $t$ is treatment time, V is urea distribution volume, and all units must be consistent.

Solution of Equation 6 for BUN build up over the intervals between HD or APD results in:

$$\mathrm{Co} = \mathrm{Ct}\ \exp[-(\mathrm{Kp} + \mathrm{Kr})ti/\mathrm{V}] + [\mathrm{G}/(\mathrm{Kp} + \mathrm{Kr})][1 - \exp[-(\mathrm{Kp} + \mathrm{Kr})ti/\mathrm{V}]] \tag{8}$$

or

$$\mathrm{Co} = \mathrm{Ct} + \mathrm{G}^{*}ti/\mathrm{V} \tag{9}$$

where Ct is post-dialysis BUN as in Equation 7, Co is pre-dialysis BUN prior to the next IHD or APD treatment, $ti$ is the interdialytic time interval, and all units must be consistent. Note that Equation 8 applies if either Kp or Kr are greater than zero, while Equation 9 applies when both are zero between the IHD or APD treatments.

In order to generalize the model and calculate the average pre-dialysis BUN or Co, it is necessary to combine Equations 6–9 and to express G as a function of the normalized protein catabolic rate (PCRn) as has been developed elsewhere [9]. The generalized expression to compute Co with any combination of frequency of IHD, APD and continuous dialysis (CD) between IHD or APD sessions (see the profiles in Figure 1) is

$$\mathrm{Co} = \left[\frac{0.184(\mathrm{PCRn} - 0.17)\mathrm{V}}{[\mathrm{spKt/V}]^{*}\mathrm{V/t}}(1 - \exp[-\mathrm{eKt/V}]^{*} \times \exp[-(\mathrm{Kp} + \mathrm{Kr})((7/\mathrm{N})1440 - t)/\mathrm{V}] + \frac{0.184(\mathrm{PCRn} - 0.17)\mathrm{V}}{\mathrm{Kp} + \mathrm{Kr}}{}^{*}(1 - \exp[-(\mathrm{Kp} + \mathrm{Kr}) \times ((7/N)1440 - t)/\mathrm{V}]\right] / [1 - \exp[-\mathrm{eKt/V}] \times \exp[-(\mathrm{Kp} + \mathrm{Kr})((7/N)1440 - t)/\mathrm{V}]] \tag{10}$$

where spKt/V is the single-pool Kdt/V or KptV (for APD); $t$ is duration of intermittent treatment sessions in minutes; $N$ is the frequency of IHD or APD per week; eKt/V is the *equilibrated* Kt/V calculated from spKt/V in accordance with Equation 11 below [8]; Kp is any CD between IHD or APD sessions; Kr is included in spKt/V and in CD intervals; and all units must be consistent.

$$\mathrm{eKt/V} = \mathrm{spKt/V}[1 - 0.6/(t/60)] + 0.03 \tag{11}$$

In the case when CD is zero, profile 1 in Figure 1 with Kp and Kr zero, during the intervals between IHD or APD sessions, the expression for Co becomes

$$\mathrm{Co} = \left[\frac{0.184(\mathrm{PCRn} - 0.17)\mathrm{V}}{\mathrm{spKt/V}^{*}\mathrm{V}/t}{}^{*}(1 - \exp[-\mathrm{eKt/V}]) + (0.184(\mathrm{PCRn} - 0.17)\mathrm{V})(7/N)1440 - t)/\mathrm{V}\right] / [1 - \exp[-\mathrm{eKt/V}]] \tag{12}$$

In the case of continuous clearance only, as in normal renal function, chronic renal failure without dialysis and CAPD, Equations 10–12 reduce to

$$\mathrm{Css} = (0.184[\mathrm{PCRn} - 0.17]\mathrm{V})/(\mathrm{Kp} + \mathrm{Kr}) \tag{13}$$

where Css is the steady-state BUN with continuous clearance.

We can now substitute Co, found from solution of Equations 10 or 12, with a specified set of modality input parameters—intermittent dialysis ± continuous dialysis—into Equation 13, and solve for the *standard* urea clearance (stdK), which results in Css equal to Co at identical PCRn. The appropriate rearrangement of Equation 13 to find stdK, where stdK = (Kp + Kr) in Equation 13, is

$$\mathrm{stdK} = 0.184[\mathrm{PCRn} - 0.17]\mathrm{V/Co} \tag{14}$$

Division of Equation 14 by V and incorporation of appropriate time constants results in

$$\mathrm{std(Kt/V)} = 1440[0.184(\mathrm{PCRn} - 0.17)]/\mathrm{Co}\ \text{daily} \tag{15a}$$

$$\mathrm{std(Kt/V)} = 7^{*}1440[0.184(\mathrm{PCRn} - 0.17)/\mathrm{Co}\ \text{weekly} \tag{15b}$$

The level of therapy defined by std(Kt/V) can also be expressed as a percentage of the normal renal reference standard in accordance with

$$\%\mathrm{ref}\ (\mathrm{Krt/V}) = 100\ [\mathrm{std(Kt/V)/ref\ (Krt/V)}] \tag{16}$$

The model is now complete. Equations 15a and b permit uniform expression of the dose of dialysis as an equivalent, normalized continuous clearance for all combinations of intermittent and continuous treatment modalities. Equation 16 permits expression of the std(Kt/V) dose as a percentage of the normal renal reference standard.

## Quantitative comparisons of treatment modalities with the std(Kt/V)

The effect of different treatment modalities or schedules on std(Kt/V) is analogous to the effect of dialyser permeability (overall permeability—area product, KoA) on clearance in a dialyser. Figure 2 depicts the family of curves relating dialyser urea clearance to blood flow rate (KdU, Qb) and KoA. Note that KdU is either primarily blood flow rate- or permeability-limited, depending on the level of KoA compared with Qb. When KoA is small relative to Qb, KdU is permeability limited and plateaus with increasing Qb.

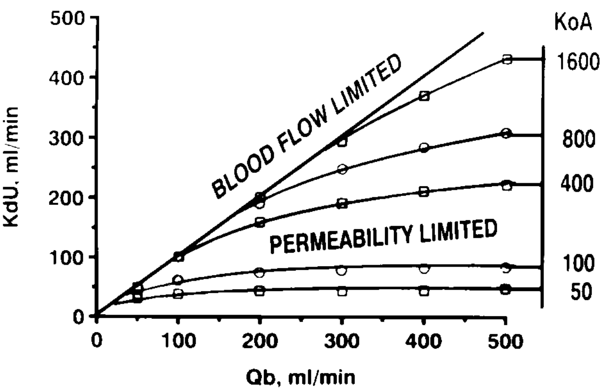

**Fig. 2.** Dialyser clearance may be limited primarily by blood flow or permeability. The dialysis dose std(Kt/V) is typically limited by time (frequency of or duration of dialyses) which is an analogue of permeability-limited dialyser clearance.

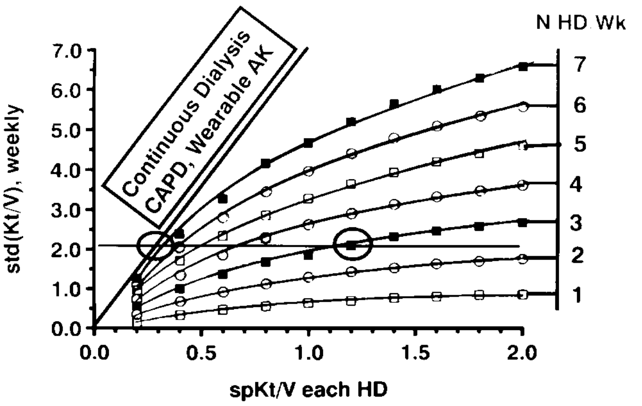

**Fig. 3.** The effect of frequency on the dose of dialysis (*t* constant at 3.5 h each dialysis): comparison with CAPD and wearable artificial kidney.

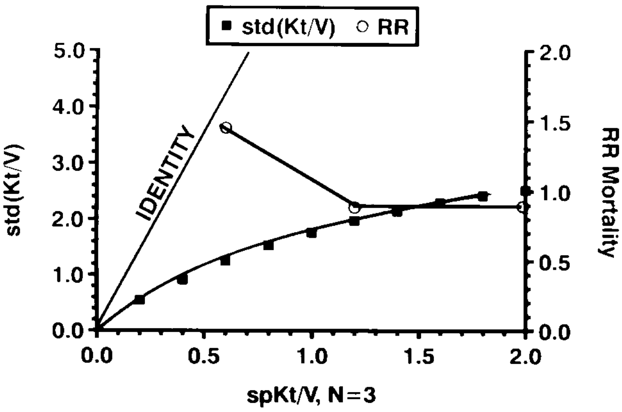

**Fig. 4.** The validity of the model-predicted plateau for std(Kt/V) with increasing spKt/V at constant *N* is supported by a similar plateau on relative risk (RR) of mortality over a similar domain of spKt/V.

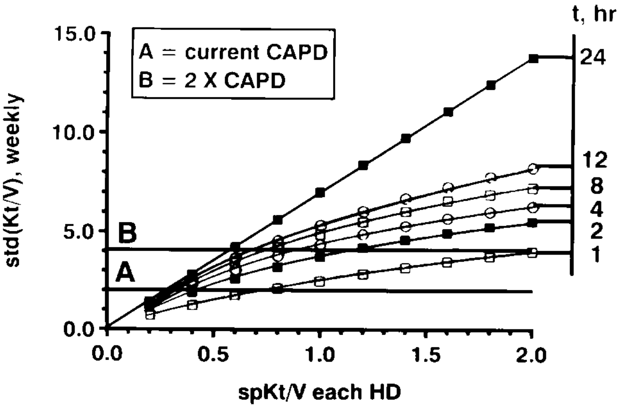

**Fig. 5.** The effect of treatment time on the standard dose of dialysis provided with daily haemodialysis: the std(Kt/V) is time limited even with daily intermittent haemodialysis.

When KoA is large compared with Qb, the clearance is blood flow limited and increases linearly with Qb.

An analogous family of curves is depicted in Figure 3, where std(Kt/V) is calculated from Equations 10–12 and 15a and b and plotted as a function of the sp(Kt/V) delivered during each dialysis and the frequency of dialysis (*N*, number per week) with *t* held constant at 3.5 h each dialysis. The identity line depicted for continuous therapy is analogous to Qb-limited KdU in Figure 1, with spKt/V an analogue of Qb. The frequency of dialysis, *N*, is analogous to KoA, and the std(Kt/V) curves reflect the limitation of dose by time for solute removal relative to that for generation. Note that at each level of *N*, as the spKt/V per treatment increases, the std(Kt/V) plateaus, reflecting increasingly inefficient solute removal as BUN falls to very low levels during each dialysis as spKt/V increases. The current recommended treatment levels, 2.0 weekly Kpt/V for CAPD and 1.2 spKt/V for thrice weekly dialysis, can be seen to be equivalent in Figure 3, providing clinical support for the modelled std(Kt/V) dosage parameter.

In Figure 4, std(Kt/V) is plotted as a function of spKt/V for thrice weekly dialysis as well as of the relative risk of mortality (RR) reported elsewhere [10]. It can be noted that both std(Kt/V) and RR plateau in the domain of $sp(Kt/V) > 1.2$, which corresponds to eKt/V of 1.03 when $t = 3.5$ h. These relationships also support the validity of the std(Kt/V) dosage parameter for quantification of intermittent and continuous therapies.

Analysis of the effect of treatment time varying from 1 to 24 h on std(Kt/V) with daily haemodialysis is depicted in Figure 5. The family of curves resulting here is analogous to those in Figure 3, where *t* was constant and *N* varied. In Figure 5, *N* is constant and *t* is varied from ultra-short (1 h) to continuous dialysis, as with a wearable kidney. The horizontal line A depicts the relationships between std(Kt/V), spKt/V and *t* for currently recommended CAPD dosage, while line B displays the relationships required if we were to double the current CAPD dose using daily HD. Line A shows that to achieve modelled therapy equivalent to weekly CAPD Kpt/V of 2.0, daily spKt/V of 0.8 is required with 1 h dialyses and of 0.3 with 8 h dialyses.

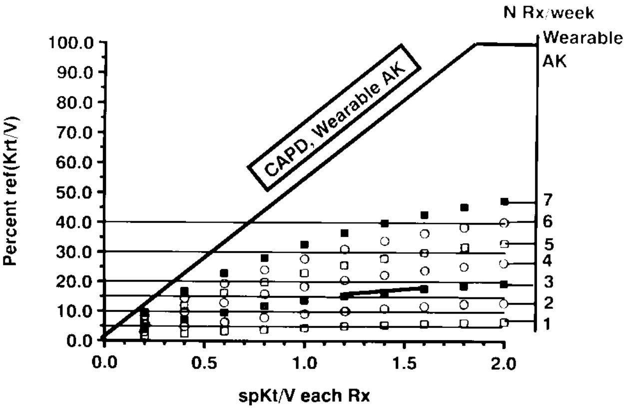

**Fig. 6.** The effect of frequency ($t = 3.5$ h) on the std(Kt/V) expressed as a percentage of normalized renal reference clearance: ref (Krt/V) = 1.85 daily, 12.96 weekly.

In order to achieve a truly new level of treatment at twice the level of current CAPD, line B indicates that daily spKt/V levels of 2.0 would be required with 1 h dialysis (unrealistic), and of 1.2, 1.0 and 0.8 with 2, 4 and 8 h dialyses, respectively. The enormous advantage of continuous clearance therapy can be seen from the identity line in Figure 5. A std(Kt/V) of 4 could be achieved with continuous urea clearance of only 20 ml/min for an average patient with V = 35 l. Although this is not feasible with CAPD, it demonstrates the modest clearance required with a continuous functioning wearable artificial kidney to achieve therapy equivalent to the substantially higher intermittent spKt/Vs required with even daily dialysis.

The percentage of ref (Krt/V) provided by IHD as a function of $N$ with $t$d constant at 3.5 h was calculated with Equation 16 from the data shown in Figure 3, with results shown in Figure 6. At spKt/V of 1.2, it can be noted that %ref (Krt/V) has risen from 5 to 15% as $N$ increased from 1 to 3. In contrast, the increase in %ref (Krt/V) as spKt/V increases from 1.2 to 1.6 with $N = 3$ is quite small, ~2%, which is consistent with the plateau on RR with spKt/V > 1.2. A potential huge increase in %ref (Krt/V) to nearly 40% is possible with daily haemodialysis, treatment time 3.5 h and spKt/V 1.2. With a continuous functioning wearable artificial kidney, the same level of therapy could be provided to the average patient (V = 35 l) with a clearance of 18 ml/min.

Although the std(Kt/V) parameter is theoretically derived, as noted above, available clinical outcome data relative to dose support its clinical relevance. A more rigorous test of its validity would require studies of clinical outcome and relative mortality over a much wider range of std(Kt/V) levels than currently available. For example, therapy protocols using daily HD with appropriate levels of $t$ and spKt/V could easily be developed to provide weekly std(Kt/V) levels (see Figure 5) ranging from 2 up to 5, or 2.5 times the maximal values achieved with thrice weekly therapy. If the modelled time constraints on std(Kt/V) depicted in Figures 3, 5 and 6 have clinical validity, the plateau on RR as a function of spKt/V with $N = 3$ in Figure 3 should not be seen when RR is examined as a function of std(Kt/V). The model prediction of several fold increases in dialysis dose with appropriate daily dialysis or a wearable artificial kidney will require appropriate clinical studies to confirm or refute marked improvement in clinical outcome as a function of std(Kt/V). The model developed here should be useful for the design and prospective prescription of dialysis doses required for such studies. Similarly, the model should be helpful for quantitative prescription of dose in emerging therapies such as CAPD augmented by IHD and continuous and intermittent HD modalities in acute renal failure.

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