

How the Web-Based *stdKt/V-calculator* Program Works

Input Values

The user enters anthropometric data from which the program estimates the urea distribution volume as 0.9 times the body water volume calculated according to the formula of Watson.¹ A different program entitled *stdKt/V-calculator enter Vdurea* allows users to enter a urea volume of distribution different from that which is predicted by the Watson formula. The user then enters values for the current treatment time on thrice weekly hemodialysis, the total weekly ultrafiltration volume, the residual urea clearance (Kru), the current single pool Kt/V (spKt/V) on thrice weekly dialysis, and the target stdKt/V. The default target stdKt/V is 2.3 as specified by the 2015 KDOQI Hemodialysis Adequacy Guideline Update²; a different value may be entered if preferred. The user also enters the pre-treatment plasma urea nitrogen level (PUN) employed in calculating spKt/V and notes whether this PUN was measured prior to the first, second, or third of the three weekly treatments.

Obtaining a Value for Kru

The required input values except for the total weekly ultrafiltration volume and Kru are routinely available in providers' monthly reports in the U.S. The total weekly ultrafiltration volume can easily be estimated from the weight removed after a two or three day intradialytic interval. However the estimation of Kru requires analysis of the urea contained in a timed urine collection which is not routinely performed and calculation of the average plasma ureaN during that collection. A number of methods have been employed for making the urine collection and calculating the corresponding average plasma urea level.

The 2015 KDOQI Hemodialysis Adequacy Guideline Update² recommends collecting urine during an entire intradialytic interval. The average plasma ureaN level can then be calculated by averaging the post-treatment plasma ureaN level at the beginning of this collection and the pre-treatment plasma ureaN level at its end. Even assuming that urea generation is constant, this calculation introduces a small error because the urea distribution volume does not

remain constant between treatments. Solute Solver (<http://www.ureaKinetics.org/>) and EuReCa app (<https://clearance.streamlit.app/>) derive values for Kru from the volume of a urine collection, collection time, and urine ureaN concentration along with dialysis prescription parameters which more precisely model the intradialytic plasma ureaN concentration.

The main practical difficulties with the method suggested by the 2015 KDOQI Hemodialysis Adequacy Guideline Update² are the burden on the patient to collect urine for a prolonged period and the requirement for two blood samples. Simpler methods for estimating Kru have therefore been proposed. Perhaps the most commonly employed is a 24 hour urine collection prior to a dialysis treatment with measurement of the pre-dialysis plasma urea level at that treatment. This predialysis plasma ureaN level can then be corrected downward based on the patient's urea reduction ratio to estimate the average plasma ureaN level during the urine collection as described by Daugirdas³ and Chin et al.⁴ The formula developed by Daugirdas³ for estimating Kru from a urine sample collected prior to a dialysis treatment and a plasma urea level obtained prior to that treatment has been shown to provide values similar to those obtained by kinetic modeling by Obi et al.⁵ To calculate Kru the formula divides the measured ureaN excretion rate during the timed urine collection by the pre-dialysis plasma ureaN concentration multiplied by the correction factor R where

$$R = 1.075 - (0.0038 \times \text{URR} + 0.059) \times (\text{duration of urine collection}) / \text{duration of the interdialytic interval}.$$

In this formula, Kru is given in ml/min of plasma water and should be multiplied by 1.08 to provide the Kru in ml/min in ml/min of plasma to enter in our program, as the program corrects the entered value down to Kru in ml/min of plasma water. Lindley et al.⁶ have more recently provided formulas which allow estimate of Kru from a timed urine collection at any point during the intradialytic interval. A variety of Kru calculators are also available on-line.

As a practical matter, the precision with which Kru is assessed has a modest effect on times predicted to achieve target stdKt/V values as shown in the Table below. Values in the Table were calculated using our program for a patient on thrice weekly hemodialysis who has a urea volume of distribution of 36 liters, an end treatment weight of 70 kg, a weekly ultrafiltration of 3 liters, and in whom 210 minutes of dialysis provides an spKt/V of 1.3. The table shows the predicted times for twice weekly dialysis to achieve a target stdKt/V of 2.3 if Kru is found to be close to 2 ml/min and close to 3 ml/min.

Presumed Kru	Predicted time to achieve stdKt/V 2.3 with twice weekly treatment
1.9	324
2.0	312
2.1	301
3.8	163
4.0	152
4.2	141

The variation in these predicted times to achieve a target stdKt/V of 2.3 does not seem significant. Patients will presumably be monitored clinically after a change to twice weekly treatment. The target stdKt/V of 2.3 is an ungraded recommendation of the 2015 Guideline Update and not a proven outcome measure which individual patients should achieve.

Adjustment of Plasma Concentrations to mg/dl of Body Water

The program assumes that the plasma urea nitrogen (PUN) concentration entered by the user is expressed in the conventional units of mg/dl of plasma. The program divides this number by 0.93 to estimate the concentration of urea nitrogen in mg/dl of plasma water. After the program has generated a profile of the urea nitrogen concentration through the weekly dialysis cycle as described below, it multiplies the profile concentrations by 0.93 to display the PUN in the conventional units of mg/dl of plasma. The program also assumes that the residual urea clearance Kru has been calculated in the conventional terms of ml/min of plasma, and

divides this number by 0.93 to estimate a residual urea clearance in terms of ml/min of plasma water.

Generation of the PUN Profile on the Current Thrice Weekly Schedule

The program first estimates the dialytic urea clearance K_d from the current values for $spKt/V$, treatment time, and urea distribution volume.

$$K_d = spKt/V \cdot V/t$$

It uses the two compartment urea distribution volume estimated from the body water volume rather than a theoretical single compartment urea distribution volume in calculating K_d from $spKt/V$. As shown by Daugirdas et al.^{7,8} this introduces only a small error for patients receiving adequate thrice weekly dialysis. The program further makes the common assumptions that:

- the urea distribution volume is divided in two compartments having a 2:1 volume ratio at the end of treatment
- that urea diffuses between these compartments at a rate which is 0.016 times the total urea distribution volume
- that fluid is removed from the smaller compartment during treatment so that the volume of this compartment is the same at the end of each treatment
- that fluid is added to the smaller compartment between treatments at a constant rate which is calculated from the weekly ultrafiltration rate.

An iterative routine then generates a profile of the plasma urea nitrogen concentration through a week of the currently prescribed thrice weekly dialysis using the dialytic urea clearance, urea distribution volume divided as described above, treatment time, weekly ultrafiltration volume, and an arbitrarily assumed urea generation rate. The program divides the week into 10080 one-minute intervals. The program first sets the urea concentration at the beginning of the cycle (immediately prior to the first of the weekly treatments) equal to the user specified PUN at the time of adequacy measurement on the current thrice weekly program. It then adjusts this value until the modeled values at the beginning and end of the week are within 0.001 mg/dl. Finally,

the program adjusts the urea generation rate to make the modeled pre-treatment PUN on the current thrice weekly prescription match within 0.1 mg/dl the measured value which the user has specified was obtained prior to the first, second, or third treatment on that prescription.

After generating the PUN profile predicted for the current thrice weekly treatment, the program uses our previously described iterative method to estimate treatment times required to achieve the specified target stdKt/V for both twice weekly and thrice weekly treatment.⁹ This method is described in our previous description of a cell phone application for calculating times required to achieve a target stdKt/V with twice and thrice weekly dialysis.⁹ The program then employs the estimated treatment times along with the previously calculated values for urea clearance and generation rate to predict weekly PUN profiles for both twice weekly and thrice weekly treatments which would provide the target stdKt/V. The program further notes whether the UF rates with these times would result in ultrafiltration rates exceeding 13 ml/kg/hr and calculates the treatment times required to reduce the ultrafiltration rate below that value. By selecting appropriate tabs in the legend the user can compare the predicted PUN profiles with twice weekly and thrice weekly dialysis to achieve the target stdKt/V or compare these profiles with the PUN profile for the current thrice weekly treatment. By selecting appropriate tabs the user can also plot the average peak (APC) and time-averaged (TAC) PUN and see estimated numeric values for the PUN at any time during the week by moving the cursor along the PUN profiles. Finally, the program uses a previously described method to calculate spKt/V values which the user would expect to see if the patient were dialyzed on the new thrice weekly and twice weekly prescriptions.⁹

Testing of the Program

The accuracy of the program was tested in two ways.

1) Evaluating the dialysis times predicted to yield a target stdKt/V for thrice weekly and twice weekly dialysis.

The cell phone application *stdKt/V Calculator* we developed to predict times required for twice weekly and thrice weekly dialysis was extensively tested against values obtained using *Solute Solver* programs available at <http://www.ureakinetics.org>. This testing was done for a set of hypothetical patients on 3X weekly dialysis with arbitrarily chosen values for urea volume of distribution, dialysis time, weekly ultrafiltration rate, residual urea clearance, and dialytic urea clearance. *Solute Solver Lite* was used to generate hypothetical patients with the chosen values for these parameters. The values of spKt/V generated by *Solute Solver Lite* for each of the hypothetical patients along with the values for urea volume of distribution, dialysis time, weekly ultrafiltration rate, and residual urea clearance were entered into the *stdKt/V Calculator* with the target stdKt/V set at the default value of 2.3 as well as at 2.1 and 2.5. The app generated values for treatment time required to achieve the target stdKt/V values for thrice weekly and twice weekly treatment. These times were then entered along with the hypothetical patients' values for urea volume of distribution, dialysis time, weekly ultrafiltration rate, residual urea clearance, and dialytic urea clearance into *Solute Solver What If* to obtain stdKt/V values by urea kinetic modeling. Results showed that the times required for thrice weekly and twice weekly dialysis generated by the cell phone app to achieve the target stdKt/V values closely corresponded to those generated by urea kinetic modeling.

The current program was first tested by entering values for a subset of the hypothetical patients used to test the cell phone app with the target stdKt/V set at the default value of 2.3. Other input values for these cases are shown in the table below.

Dialysis Parameter	Values Employed in Testing
Urea Volume of Distribution (liters)	approximately 20, 30, 50
Dialysis Time (min)	180, 240, 300
Weekly UF (liters/week)	7
Kru (ml/min)	0, 2, 4
Dialytic Urea Clearance (ml/min)	approximately 200, 250, 300

Among these hypothetical cases, 18 were discarded because the spKt/V value on the current thrice weekly prescription would be above 2.5. Times required for thrice weekly and twice weekly dialysis were therefore predicted for 63 cases yielding a total of 126 predicted times. *Solute Solver What If* did not provide comparison times when calculations for either the thrice weekly or twice weekly treatment in 21 instances. The new program predicted the same treatment times for thrice weekly and twice weekly dialysis as the cell phone app and *Solute Solver What If* for the other 105 instances.

The new program was further tested by entering values for a subset of 11 of the same cases with the weekly UF value changed to zero L/week and for a subset of the 20 of the same cases with weekly UF value remaining at 7 L/week and the target stdKt/V changed to 2.5. The new program again predicted the same treatment times for thrice weekly and twice weekly dialysis as the values generated by the cell phone app which had been found equal to those generated by *Solute Solver What If*.

1) Evaluating the PUN profiles produced by the new program

PUN values generated by the new program were also compared with PUN values generated by *Solute Solver* programs. For the current thrice weekly program, the peak PUN (day one, pre-treatment), time averaged (TAC) PUN, and midweek post treatment PUN values generated by the current program were compared with values generated by *Solute Solver Lite*. PUN values generated by the current program were obtained by moving the cursor as close as possible to the appropriate time along the PUN profile. Results for the same 105 hypothetical instances for which times obtained using the current program were tested showed:

Parameter	Peak PUN	TAC PUN	Post-Rx PUN Midweek
Current Program / Solute Solver (mean ± sd)	1.000 ± 0.005	1.000 ± 0.002	1.074 ± 0.073

For the new thrice weekly and twice weekly prescriptions, the PUN values on day one and on day 3 for thrice weekly and on day 4 for twice weekly prescriptions were compared with PUN values generated by *Solute Solver What If*. PUN values were again compared for the same 105 hypothetical instances for which times obtained using the current program were tested. This comparison showed:

Parameter	Pre-RX Day 1	Post-Rx Day 1	Pre-Rx Day 3 or 4	Post Rx Day 3 or 4
Current Program / Solute Solver (mean \pm sd)	0.995 \pm 0.007	1.050 \pm 0.062	1.000 \pm 0.007	1.050 \pm 0.062

These results indicated that the program would provide users with an appropriate impression of the extent to which PUN values would rise if treatment times were shortened.

References

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