

Equations for Normalized Protein Catabolic Rate Based on Two-Point Modeling of Hemodialysis Urea Kinetics¹

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(J. Am. Soc. Nephrol. 1996; 7:780-785)

ABSTRACT

The normalized protein catabolic rate (PCRn) can be calculated from predialysis and postdialysis BUN measurements in patients receiving intermittent dialysis. This measure of net protein catabolism, adjusted for body size, is a useful clinical measure of nutrition that correlates with patient outcome and, in patients who are in nitrogen balance, is a reasonable estimate of dietary protein intake. Whereas simplified formulae that estimate the per-treatment dose of hemodialysis, expressed as Kt/V_{urea} (Kt/V), are in common use, simplified methods for determining PCRn have only recently appeared. In the study presented here, equations were derived for calculating PCRn from the predialysis BUN and Kt/V . The equations were of the general form: $PCRn = C_0 / (a + bKt/V + c/(Kt/V)) + 0.168$, where C_0 is the predialysis BUN in mg/dL. Three sets of coefficients were developed for patients dialyzed thrice weekly: one for patients dialyzed after the long interval at the beginning of the week, one for patients dialyzed at midweek, and the third for patients dialyzed at the end of the week. Two similar sets of coefficients were developed for patients dialyzed twice weekly. For patients with remaining function in the native kidney remnant, equations were developed and refined for upgrading PCRn by adjusting C_0 upward. The equations were validated by comparing the calculated PCRn with PCRn determined by a formal iterative model of urea kinetics in a series of 119 dialyses in 51 patients dialyzed thrice weekly ($r = 0.9952$; mean absolute error, $1.97 \pm 1.39\%$) and in a series of 71 dialyses in 25 patients dialyzed twice weekly ($r = 0.9956$; mean absolute error, $2.17 \pm 1.56\%$). These simple yet accurate equations should be useful in epidemiologic studies or in clinical labo-

ratories where limited data are available for each patient or when iterative computer techniques cannot be applied.

Key Words: PCRn, nutrition, Kt/V , protein intake, simplified calculation

Models of urea kinetics during therapeutic hemodialysis currently provide useful clinical measurements that play an important role in helping clinicians judge the performance of dialysis equipment, net protein catabolism, risk of dying, and the adequacy of dialysis in individual patients. The most popular indices derived from urea modeling are Kt/V_{urea} (Kt/V), a measure of the dose of each dialysis that correlates positively with patient overall health and longevity, and the normalized protein catabolic rate (PCRn), an individualized measure of protein intake or catabolism (1-3). Paralleling efforts to improve the precision and accuracy of these modeled variables have been efforts to simplify their measurements so that dialysis centers and clinical laboratories can more easily provide them to clinicians and can provide them at more frequent intervals for each patient. Several equations that are currently available for estimating Kt/V from a predialysis and a postdialysis BUN give reasonably quick estimates that are usually well within 5% of the value provided by a more complex iterative approach requiring a computer or programmable calculator (4-6). A quick and simple equation describing PCRn, however, has been elusive; recently developed formulae are either inaccurate (7) or limited in their application (8). Efforts to generate such an equation have been hampered by the need to measure a third BUN before the next dialysis to estimate urea generation (9-11). Careful analysis of the origin of PCRn, however, has shown that the third BUN measurement is not necessary because PCRn can be calculated from the absolute value of the predialysis BUN and the dialysis dose, Kt/V (6,12,13).

Nomograms representing the relationship between predialysis BUN, Kt/V , and PCRn were derived previously by using a computer-generated two-BUN, variable-volume, single-pool model of hemodialysis urea kinetics (1,12,14,15). When Kt/V is constant, the relationship between steady-state C_0 and PCRn is essentially linear with a common x-axis intercept. We previously devised a graphical nomogram approach to urea kinetic modeling that does not require the use of computer software (15). By using this method, Kt/V calculated from a simplified formula (5) or read from a graph (15) can be applied to another graph derived from two-BUN modeling to estimate the PCRn. Because graphs are difficult to apply to large data sets, we examined the Kt/V isopleths in the PCRn nomo-

¹ Received December 8, 1994. Accepted January 8, 1996.

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1046-6673/0705-0780\$03.00/0

Journal of the American Society of Nephrology
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grams and found several uniform properties that allowed derivation of explicit mathematical formulas to approximate the PCRn values ordinarily read from the graph.

METHODS

Linear equations were derived for steady-state midweek predialysis BUN measurements (C_0) in mg/dL of whole serum as a function of PCRn in g protein/kg normalized body weight per day at constant values of Kt/V , ranging from 0.4 to 2.0 per dialysis, using a technique similar to that described by Gotch (12). Normalized body weight is defined as $V/0.58$, where V is the volume of urea distribution (9). The technique for generating the linear equations uses a single-compartment, variable-volume mathematical simulation of hemodialysis urea kinetics that requires multiple iterations to resolve C_0 (11). Because the predialysis BUN level (C_0) varies depending on the day of the week, the slope of the line relating C_0 to PCRn also depends on the day of the week. C_0 values were calculated at two levels of PCRn (1.0 and 2.0 g/kg per day) to generate linear equations of the form $y = ax + b$, where y is C_0 and x is PCRn. Assumptions were $V = 35$ L, $t = 180$ min, and weight gain = 1.0 kg/day, but the equations have previously been shown to have little variation in slope or intercept and are essentially linear over a wide range of values for PCRn, dialyzer clearance, dialysis time, V , and ultrafiltration rates at each level of Kt/V (14). Additional equations were derived relating both first-of-week predialysis BUN levels and end-of-week predialysis BUN levels to PCRn for a series of Kt/V values ranging from 0.4 to 2.0/dialysis dose in increments of 0.2/dialysis. Another two sets of equations were developed using the same technique for patients dialyzed twice weekly. For each of the latter sets, C_0 was calculated for Kt/V values ranging from 0.4 to 4.0/dialysis.

The lines relating C_0 to PCRn have a common x-axis (PCRn) intercept at 0.168 g/kg per day (Figure 1) but the slopes vary with Kt/V and with the dialysis schedule and the day of the week (16). For each of the five sets of isopleths, representing the two schedules and days of the week, the slopes of the C_0 versus PCRn lines were plotted as a function of Kt/V and the data were fit to a series of equations using statistical curve-fitting methods (Figure 2).

Urea kinetics were modeled during 119 dialyses in 51 patients randomly selected from a hemodialysis center (University Dialysis Clinic, Sacramento, CA) that applies high-flux treatments for 2 to 5 h three times per week. An additional 71 dialyses were modeled in 25 patients from the same clinic who were dialyzed twice weekly. An additional 50 dialyses were modeled in 22 patients with significant residual renal function who were dialyzed thrice weekly. The volume of urea distribution varied from 16 to 80 L, dialyzer clearance varied from 171 to 319 mL/min, dialysis time varied from 120 to 255 min, and interdialysis weight gain varied from 0.1 to 3.9 L/day. Blood samples and weights were obtained before dialysis and immediately after dialysis. The BUN level measured by the clinical laboratory was modeled using a computer program for single-compartment, variable-volume urea kinetics described previously (17). Residual renal function was measured from 24-h urine collections obtained between dialyses and analyzed for urea nitrogen concentration by the clinical laboratory. The mean BUN during the collection was computed from the concentration obtained after dialysis and the single-pool model of urea kinetics.

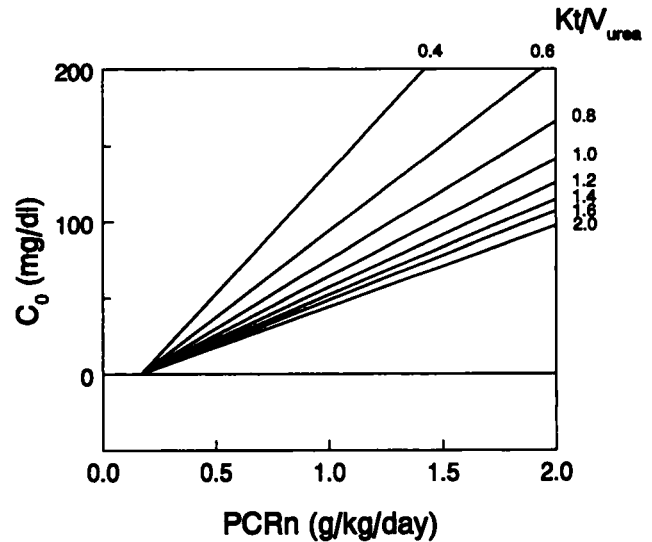


Figure 1. Each isopleth represents the near-linear relationship between C_0 , in mg/dL of whole serum, and PCRn when Kt/V is held constant. C_0 was calculated using the single-pool, variable-volume model of hemodialysis urea kinetics for patients dialyzed at midweek, three times per week. Additional linear equations were developed for the beginning-of-week dialysis, for the end-of-week dialysis, and for the first and second dialyses in patients treated twice weekly (graphs not shown).

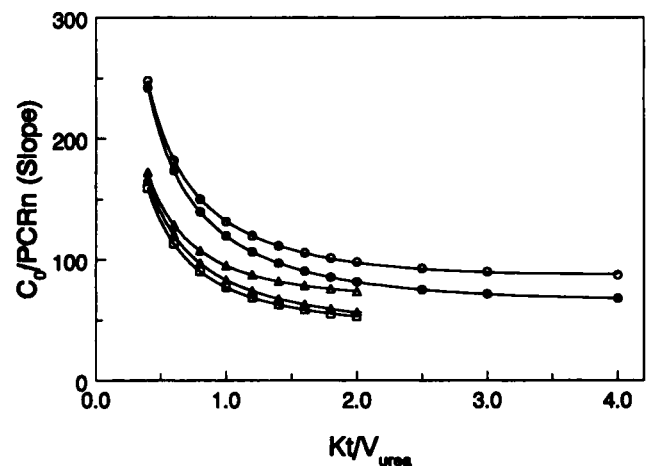


Figure 2. The slopes of the C_0 versus PCRn lines depicted in Figure 1 and other schedules are plotted as functions of Kt/V . The best fits of Equations 1 through 5 to the data are shown as solid lines. The open circles are modeled after a 4-day interval and the solid circles are modeled after a 3-day interval in patients dialyzed twice weekly. The open triangles are modeled at the beginning of the week, the solid triangles at midweek, and the open squares at the end of the week in patients dialyzed three times per week.

Equations for adjustment of C_0 in patients with significant residual urea clearance (K_r) were derived empirically using a simple equation that related the adjustment of C_0 to both K_r/V_{urea} and to Kt/V . The new value for C_0 (C'_0), when

applied to above equations, gave values for PCRn that compared favorably with PCRn obtained from the formal urea model.

Selection of the terms and coefficients of best fit for Equations 1 through 7 was done by a nonlinear least-squares curve-fitting technique that uses the Levenberg-Marquardt algorithm (18,18a). The Pearson correlation coefficient (r) was used for statistical comparisons of theoretical curves and patient data.

RESULTS

Figure 1 shows the set of linear isopleths describing midweek C_o as a function of PCRn for Kt/V values from 0.4 to 2.0. Note the common x-axis intercept at 0.168 g/kg per day. The slope of each C_o versus PCRn isopleth is plotted in Figure 2 as a function of Kt/V . The five sets of isopleths represent different dialysis days of the week for patients treated three times per week and for patients treated twice weekly. The equation of best fit for all of these graphs is $y = a + bx + c/x$, where y is the slope of each C_o versus PCRn isopleth and x is Kt/V . As is evident from the Figures, the empirically derived equations fit the slopes quite well with values for r^2 greater than 0.9999. The following is a listing of the simplified formulas for PCRn, with corresponding coefficients for a , b , and c :

For thrice-weekly dialysis:

beginning-of-week:PCRn =

$$C_o/[36.3 + 5.48Kt/V + 53.5/(Kt/V)] + 0.168 \quad (1)$$

midweek:PCRn =

$$C_o/[25.8 + 1.15Kt/V + 56.4/(Kt/V)] + 0.168 \quad (2)$$

end-of-week:PCRn =

$$C_o/[16.3 + 4.30Kt/V + 56.6/(Kt/V)] + 0.168 \quad (3)$$

For twice-weekly dialysis:

beginning-of-week:PCRn =

$$C_o/[48.0 + 5.14Kt/V + 79.0/(Kt/V)] + 0.168 \quad (4)$$

end-of-week:PCRn =

$$C_o/[33.0 + 3.60Kt/V + 83.2/(Kt/V)] + 0.168 \quad (5)$$

For patients with significant residual function, C_o was adjusted upward according to the following empirically derived equation for patients dialyzed three times per week:

$$C'_o = C_o[1 + (0.70 + 3.08/(Kt/V))K_r/V] \quad (6)$$

The following equation was applied to patients dialyzed twice weekly:

$$C'_o = C_o[1 + (1.15 + 4.56/(Kt/V))K_r/V] \quad (7)$$

C'_o and C_o are expressed in mg/dL, K_r in mL/min, and V in L.

Table 1 shows the results of applying Equations 1 through 3 to a set of data from patients dialyzed on

TABLE 1. Simplified calculation of PCRn compared with formal modeling in patients with no residual clearance who were dialyzed three times/week (mean \pm SD)

Parameter	Beginning-of-Week (N = 51)	Midweek (N = 44)	End-of-Week (N = 24)
Mean % Error	-0.48 \pm 2.30	-1.91 \pm 1.93	-1.27 \pm 1.62
Mean % Error	1.72 \pm 1.60	2.32 \pm 1.42	1.85 \pm 0.89
Max % Error	8.39	5.92	3.78
r	0.9930	0.9954	0.9982

different days of the week, compared with PCRn values derived from formal modeling. Table 2 shows a similar comparison for Equations 4 and 5 in patients dialyzed twice weekly. The mean absolute error (mean |% error|) for both sets of data was $< 2.5\%$, well within the clinically acceptable range.

Figure 3 shows the correlation between PCRn derived from formal two-point, single-pool, variable-volume modeling (x-axis), and PCRn calculated from Equations 1 through 3 (y-axis). The data were taken from 119 hemodialyses in 51 patients with no residual function who were dialyzed three times weekly. Figure 4 shows a similar plot of PCRn values for 71 hemodialyses in 25 patients without residual function (or in whom residual function was ignored) who were dialyzed only twice weekly. Figure 5 shows a similar plot for 50 dialyses in 22 patients with significant residual native kidney function. A graph (not shown) for 32 dialyses in 13 patients with significant residual function who were dialyzed twice weekly was similar ($r = 0.9926$). PCRn values derived from formal modeling correlated well with PCRn calculated from Equations 1 through 7.

DISCUSSION

Both Kt/V and PCRn require little data to calculate and both have relatively universal applicability independent of patient size. Because Kt/V is derived from the ratio of predialysis to postdialysis BUN, little else is required to calculate it (2). Less appreciated is the fact that PCRn can also be determined from simple measurements of BUN before and after a single dialy-

TABLE 2. Simplified calculation of PCRn compared with formal modeling in patients with no residual clearance who were dialyzed twice/week (mean \pm SD)

Parameter	Beginning-of-Week (after a 4-day interval) (N = 51)	Last-of-Week (after a 3-day interval) (N = 20)
Mean % Error	2.08 \pm 2.07	1.29 \pm 1.58
Mean % Error	2.43 \pm 1.64	1.53 \pm 1.35
Max % Error	6.52	5.41
r	0.9951	0.9964

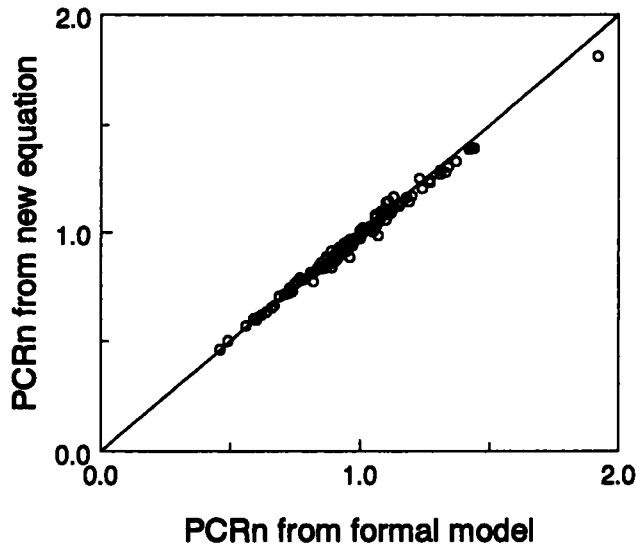


Figure 3. Comparison of PCRn derived from formal modeling to PCRn calculated using Equations 1, 2, and 3 during 119 hemodialyses in 51 patients with no residual kidney function, dialyzed three times per week. Data were obtained during 51 hemodialyses at the beginning of the week, during 44 hemodialyses at midweek, and during 24 hemodialyses at the end of the week. The solid line is the line of identity. $r = 0.9952$.

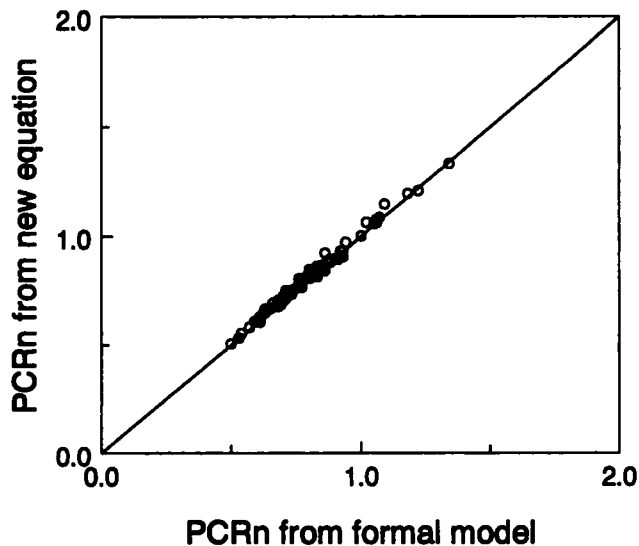


Figure 4. Similar to Figure 3. Equations 4 and 5 were applied to data from 71 hemodialyses in 25 patients with no residual kidney function, dialyzed twice weekly. Data were from 51 hemodialyses following a 4-day interval and from 20 hemodialyses after a 3-day interval between dialyses. $r = 0.9956$.

sis. A third BUN measurement is not required to measure either urea nitrogen generation rate or PCRn. In contrast to the urea nitrogen generation rate, and despite the expression of results in g/kg normalized body weight, no measure of body weight or of the

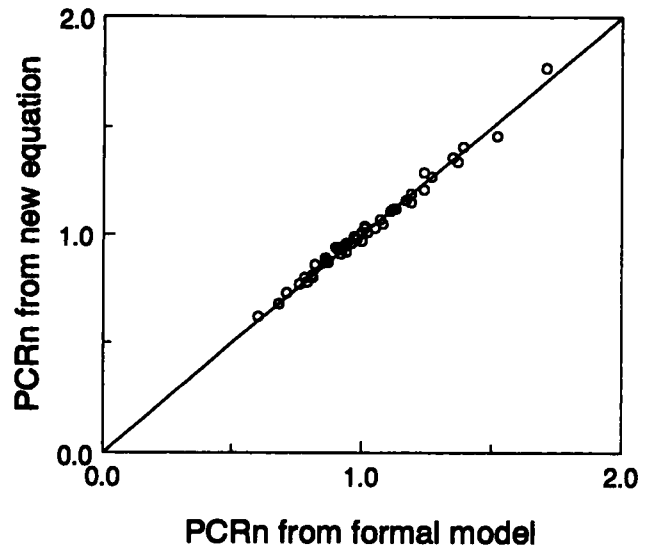


Figure 5. Similar to Figure 3. Equations 1, 2, 3, and 6 were applied to 50 hemodialyses in 22 patients with significant K_t (mean, 3.1; range, 0.5 to 6.4 mL/min), dialyzed three times per week; 31 hemodialyses were at the beginning of the week, nine at midweek, and ten at the end of the week. $r = 0.9899$.

patient's urea volume is required to determine PCRn. This seemingly paradoxical conclusion is based on the mathematical association of PCRn with the absolute value of the predialysis BUN (19). Once the delivered dose of dialysis is fixed, the BUN level achieved depends almost entirely on PCRn, a parameter that is independent of body size.

Because predialysis BUN concentration (C_0) varies depending on the day of the week it is measured, separate formulae for PCRn are required for each dialysis day of the week in patients dialyzed by the usual thrice- or (rarely) twice-weekly schedule. This approach can be simplified to a single equation by using time-averaged BUN (TAC) but TAC is not easily measured or estimated without use of a calculator or iterative computer program (11).

The Kt/V isopleths relating C_0 to PCRn at constant Kt/V as depicted in Figure 1 are essentially linear and vary surprisingly little over a wide range of values for Kt/V , PCRn, and ultrafiltration rates (14). The slight variance in linearity and relative constancy of the slopes and intercepts justifies the use of linear equations to calculate PCRn from predialysis BUN when Kt/V is known. The equations have advantages, compared with graphs that describe a limited number of Kt/V isopleths and require visual interpolation to determine most real values. The equations can also be incorporated into spreadsheets and computer programs for immediate calculation and reporting of PCRn without need for recursive programming.

The effort required to derive an equation to accurately resolve PCRn as a function of Kt/V and C_0 was made simpler by the common intercept of the Kt/V

isopleths shown in Figure 1. This intercept is the constant in the equation for PCRn expressed as a function of G and V ($\text{PCRn} = 5.42G/V + 0.168$) (20) and represents protein catabolism that is not related to urea appearance (when urea generation is zero). This catabolic rate, like the remainder of PCRn, is considered to vary with patient size or volume (9) and can therefore be expressed in protein nitrogen equivalents factored for patient size.

The method used to generate the linear equations depicted in Figure 1 is identical to that published by Gotch (12). The previously described graph—which was generated only for patients dialyzed at midweek, thrice weekly—is superimposable on our graph generated from Equation 2 (Figure 1) only if the predialysis BUN values in the previous graph are interpreted as serum water concentrations (approximately 7% higher than whole serum concentrations). In contrast to Kt/V , proper interpretation of PCRn in these equations and graphs requires that whole serum concentrations of urea nitrogen, such as those described in this study, must be distinguished from the serum water concentrations described in previous publications. This distinction has rarely been made previously.

When using a single-compartment model to calculate Kt/V , and one of Equations 1 through 5 to calculate PCRn, two potential (but avoidable) sources of error must be kept in mind. The first source of error is the result of urea rebound after dialysis. It is now clear that Kt/V computed from a predialysis BUN measurement and a BUN measurement taken immediately after dialysis, will underestimate the whole-body or effective Kt/V by 10 to 25%, depending partly on the efficiency of dialysis but also depending on patient factors (19). The effective Kt/V can be derived from an "equilibrated" postdialysis BUN but the impracticality of waiting for up to an hour after dialysis for blood sampling has led to several estimation methods. One can assume an average disequilibrium coefficient for all patients and estimate the rebound based on the dialysis time and dialyzer clearance-to-patient urea volume ratio (21). Alternatively, the single-pool Kt/V can be reduced by 10% for a low-efficiency treatment or by 20% for a high-efficiency treatment (15). When the reduced value for Kt/V is used in conjunction with the actual predialysis BUN measurement, the present equations will give a more accurate (lower) value for PCRn.

The second potential source of error in using these equations and graphs (which applies equally to more formal modeling) is failure to incorporate residual renal function into the calculation of PCRn. The use of Equations 1 through 5 without adjustment for K_r will greatly underestimate PCRn. To prevent this error, an accounting of urea nitrogen losses by the remnant kidney must be included in the method for calculating PCRn. Similarly, Kt/V is often adjusted to reflect the combined effect of dialysis plus residual kidney function (K_r) (12,15). The new " K " in the adjusted Kt/V is a virtual clearance that represents the dialyzer clear-

ance required to achieve the same predialysis BUN measurement in the patient if residual clearance were reduced to 0. This method fails, however, in some patients with high PCRn and high K_r , in whom increasing dialyzer clearance to infinity (total urea removal from the patient) fails to bring the predialysis BUN down to the level achieved by the combined effect of dialysis and residual function. As an alternative to adjusting Kt/V in patients with residual function, we adjusted C_0 to reflect the level that would be reached if K_r were absent. This method requires an estimate of V but is insensitive to errors in V , so anthropometrically determined values are adequate. When the adjusted value for C_0 was entered into Equations 1 through 5, the calculated PCRn was highly accurate, as is shown in Figure 5.

Because it is factored for patient size (V), PCRn allows comparison of protein nutrition among patients but for the same reason it cannot be used alone to prescribe a diet. A measure of PCR [$\text{PCRn}(V/0.58)$] expressed in g protein/day is required. To convert to PCR, a value for V can be obtained from previous formal modeling of urea kinetics or from anthropometric formulae. With extremely obese or edematous patients, care must be taken to estimate V and PCR accurately.

In summary, a series of five equations were developed for patients who are in a steady state of nitrogen balance to approximate PCRn values obtained from more formal iterative modeling, including the adjustments for residual clearance. Only two BUN measurements are required, but unique equations are necessary for dialyses evaluated at the first, middle, or end of the week and for dialysis scheduled two times versus three times per week. These simple yet highly accurate equations can be applied in the course of quality-assurance programs or in epidemiologic studies to obtain values for PCRn when only limited data concerning the dialysis treatments is available.

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