Extracorporeal Therapy Requirements for Patients with Acute Renal Failure

WILLIAM R. CLARK,∗† BRUCE A. MUELLER,§ MICHAEL A. KRAUS,† and WILLIAM L. MACIAS®†

∗Renal Division, Baxter Healthcare Corp., McGaw Park, Illinois; †Nephrology Division,′ Department of Medicine, Indiana University School of Medicine, Indianapolis, Indiana; §Department of Pharmacy Practice, Purdue University School of Pharmacy, West Lafayette, Indiana; and †Eli Lilly and Company, Indianapolis, Indiana.

Abstract. Renal replacement therapy (RRT) requirements for critically ill patients with acute renal failure (ARF) depend on numerous factors, including the degree of hypercatabolism, patient size, and desired level of metabolic control. However, the current practice at many institutions is to prescribe generally similar amounts of RRT to ARF patients essentially without regard for the above factors. In this study, a computer-based model designed to permit individualized RRT prescription to ARF patients was developed. The critical input parameter is the desired level of metabolic control, which is the time-averaged BUN (BUNa) or steady-state BUN (BUNs) for intermittent hemodialysis (IHD) or continuous RRT (CRRT), respectively. The basis for the model was a group of 20 patients who received uninterrupted CRRT for at least 5 days. In these patients, the normalized protein catabolic rate (nPCR) increased linearly (r = 0.974) from 1.55 ± 0.14 g/kg per day (mean ± SEM) on day 1 to 1.95 ± 0.15 g/kg per day on day 6. The daily urea generation rate (G), determined from the above linear relationship, was utilized to produce BUN versus time curves by the direct quantification method for simulated patients of varying dry weights (50 to 100 kg) who received variable CRRT urea clearances (500 to 2000 ml/h). Steady-state BUN versus time profiles for the same simulated patient population treated with IHD regimens (K = 180 ml/min, T = 4 h) of variable frequency were generated by use of a variable-volume, single-pool kinetic model. From these profiles, regression lines of required IHD frequency (per week) versus patient weight for desired BUNs values of 60, 80, and 100 mg/dl were obtained. Regression lines of required CRRT urea K (ml/h) versus patient weight for desired BUNs values of 60, 80, and 100 mg/dl were also generated. For the attainment of intensive IHD metabolic control (BUNs = 60 mg/dl) at steady state, a required treatment frequency of 4.4 dialyses per week is predicted for a 50-kg patient. However, the model predicts that the same degree of metabolic control cannot be achieved even with daily IHD therapy in patients ≥ 90 kg. On the other hand, for the attainment of intensive CRRT metabolic control (BUNs = 60 mg/dl), required urea clearance rates of approximately 900 ml/h and 1900 ml/h are predicted for 50- and 100-kg patients, respectively. This model suggests that, for many patients, rigorous azotemia control equivalent to that readily attainable with most CRRT can only be achieved with intensive IHD regimens. Following prospective clinical validation, this methodology may be a useful RRT prescription tool for critically ill ARF patients. (J Am Soc Nephrol 8: 804–812, 1997)
(CVVHD) (10,11), and continuous arteriovenous hemodialysis (CAVHD) (12,13), to provide improved metabolic control. To date, no prospective study evaluating the effect of continuous renal replacement therapy (CRRT) intensity on outcome has been reported. Therefore, recommendations for target levels of metabolic control in patients treated with CRRT currently do not exist as they do for IHD. However, retrospective data (8) suggest that a positive correlation exists between CRRT intensity and clinical outcome.

The current practice at many institutions is to prescribe generally similar amounts of RRT to ARF patients essentially without regard for such factors as patient size and degree of hypercatabolism. However, the ability to prescribe either IHD or a CRRT on an individualized basis may be desirable. In an attempt to predict the metabolic control provided by RRT to a broad spectrum of patients with ARF, we have developed a computer-based model. This model, the basis of which is a series of critically ill ARF patients who received CVVH at our institution, utilizes both therapy-specific and patient-specific parameters as inputs to estimate metabolic control over time. This prospective approach may allow for the individualization of RRT administration to critically ill patients with ARF and permit the prescription of regimens that more effectively achieve metabolic control targets.

Materials and Methods

**CVVH Patient Population and Protocol**

Oliguric patients with ARF who received CVVH at Indiana University Hospital were eligible for inclusion. The major inclusion criteria were (1) adequate data collection; (2) urine output of less than 400 ml/day; and (3) minimum of 5 uninterrupted days of CVVH therapy. An uninterrupted day of therapy was defined as a 24-h period (6 a.m. to 6 a.m.) during which CVVH was discontinued for < 60 min and/or the ultrafiltrate production rate was > 22 l/day.

The standard CVVH operating protocol at our institution was observed for all patients (7). All patients received CVVH in an intensive care unit. The major features of the extracorporeal circuit included a polysulfone hemofilter (Amicon-20; W.R. Grace and Company, Danvers, MA), a roller blood pump (RS-7800; Renal Systems, Minneapolis, MN), and an ultrafiltrate pump (Flo-gard; Baxter Healthcare, Deerfield, IL). The blood pump setting was between 150 and 200 ml/min whereas the ultrafiltrate pump was utilized to maintain an hourly ultrafiltrate production rate of approximately 1000 ml/h. Bicarbonate-based replacement fluids were administered in a predilution mode. The duration of use of each hemofilter was limited to 48 h. Before the initiation of CVVH, clinical and biochemical data were collected. Subsequently, biochemical data, including BUN values, were obtained at 6-h intervals. Complete fluid intake and output data, including 24-h ultrafiltrate production rates, were measured daily.

**Generation of nPCR Versus Day of Therapy Curve**

Serial BUN values from a group of patients who received at least 5 days of uninterrupted CVVH therapy were used to construct a standardized curve of normalized protein catabolic rate (nPCR) versus day of therapy. The nPCR was determined for each patient from the total daily nitrogen appearance rate as a function of \( G_n \), the urea generation rate, and the non-urea nitrogen generation rate, \( G_{nu} \). The value of \( G_n \) was estimated for each patient by a urea mass balance technique originally described by Feinstein et al. (14) and recently utilized by our group (15). Based on previous studies (16–18) in relatively small numbers of patients, \( G_{nu} \) was estimated to be 1.5 g nitrogen per day in each patient.

**CRRT Computer Model**

The CRRT computer model was based on the direct dialysis quantification (DDQ) equation of Malchesky et al. (19):

\[
V_{UF} \cdot C_{ur} = V \cdot (C_j - C_{j+1}) + G_u \cdot t
\]

In this equation, \( V_{UF} \) is the ultrafiltrate volume (liters), \( C_{ur} \) is the mean ultrafiltrate urea nitrogen concentration (mg/dl), \( C_j \) and \( C_{j+1} \) are the initial and final BUN values (mg/dl), respectively, and \( t \) is the treatment interval length (h). \( C_{ur} \) was calculated as the mean of \( C_j \) and \( C_{j+1} \) from an assumed urea sieving coefficient of 1.0.

The DDQ equation was incorporated into a computer program designed to predict the degree of azotemia control as a function of the amount of delivered therapy. Programming was done on a Macintosh II personal computer (Cupertino, CA) in FORTRAN (MacFortan II; Absoft Co., Rochester Hills, MI) language. The program utilized 12-h increments for calculation purposes over a 6-day treatment period. During each 12-h time increment, the DDQ equation was solved for \( C_{j+1} \) in terms of \( V_{UF} \), \( C_j \), and \( G_u \). For a specific body weight (W), the value of G was derived from the standardized nPCR curve by use of the following equation:

\[
nPCR = 6.25 \cdot \left( 1.44 \cdot G_u + G_{nu} \right)/BW
\]

**CRRT Patient Simulations**

The program was used to predict the azotemia control over a 6-day treatment period for simulated patients. The primary input variables for the program were patient dry weight (\( W_d \)) and ultrafiltrate production rate (UFR). Six different values of \( W_d \) were evaluated: 50 kg, 60 kg, 70 kg, 80 kg, 90 kg, and 100 kg. Likewise, six different values of UFR, which was assumed to equal convective urea clearance (K), were used: 500 ml/h, 750 ml/h, 1000 ml/h, 1250 ml/h, 1500 ml/h, and 2000 ml/h. These weight and UFR ranges account for the vast majority of situations encountered in clinical practice. For all simulated regimens, the initial BUN was assumed to be 130 mg/dl. The pre-treatment value of V was assumed to be 60% of initial body weight (\( W_d \)). To simulate correction of volume overload over the treatment period, \( W_d \) was assumed to be equal to 0.9 - \( W_d \), and was achieved at the end of the 6-day treatment period. Weight loss was assumed to be entirely the result of correction of volume overload and occurred at a constant rate. Adjustment of V occurred after each 12-h increment, such that at the end of the entire treatment period, V approximated 0.56 - \( W_d \).

The program’s output for each 12-h increment was the BUN at the end of that time interval (\( C_{j+1} \)). For the subsequent time interval, V was adjusted as described above. In addition, the BUN calculated for the end of the preceding interval became the initial BUN for the subsequent interval. In this way, serial BUN values were determined for the entire analysis period.

The evaluation of six different K and \( W_d \) values produced a total of 36 separate simulated CRRT regimens. By the completion of nearly all of the regimens, a steady state was reached, with the BUN on day 6 differing from the day 5 BUN by less than 5%. For these regimens, the day 6 BUN was considered the steady-state BUN (BUNs).
**IHD Patient Simulations**

For the IHD simulations, steady state not only with respect to nPCR but also to volume status was assumed to have been reached by day 6. To estimate the rate of protein catabolism during the week-long simulated steady-state period, the day 6 nPCR value from the nPCR standardized curve was utilized. Total weekly fluid administration was estimated to be 0.2-W_d, or approximately 0.03-W_d per day. For a patient with a dry weight of 70 kg, this corresponds to a fluid administration rate of 2 l/day. The additional assumptions for the IHD simulations were: symmetric dialysis schedule; K = 180 ml/min; T = 4 h; and dialysis frequency = three to seven times per week.

With values of nPCR, V, K, T, and IHD frequency known or assumed, a variable-volume, single-pool model (20) was used to generate BUN versus time profiles over the same dry weight range (50 to 100 kg) used in the CRRT simulations. Interdialytic and intradialytic urea mass balances were solved simultaneously first to determine peak BUN (BUN_a) and trough BUN values. Subsequently, the time-averaged BUN (BUN_d) for each regimen was calculated. From these data, a BUN_a versus IHD frequency curve was generated for each simulated patient weight.

**Steady-State Analysis of RRT Azotemia Control**

Steady-state azotemia control in patients with renal failure has been shown to vary directly with the rate of protein catabolism and inversely with therapy dose (20,21). For CRRT patients, Clark et al. (21) demonstrated that the relationship between BUN_a and the ratio nPCR/(KT/V)_d is linear, where (KT/V)_d is the daily normalized dose of therapy. Therefore, data from all simulated CRRT regimens in which steady state was reached were utilized collectively to assess the relationship between BUN_a, and nPCR/(KT/V)_d. A similar assessment was performed to determine the relationship between BUN_a and nPCR/(KT/V)_d from the IHD simulations.

**Results**

**Standardized Curve of nPCR Versus Day of Therapy**

The standardized curve of nPCR versus day of therapy (Figure 1) was generated from 20 patients who received at least 5 days of uninterrupted CVVH therapy. For these patients, nPCR increased linearly over the initial 6 treatment days from 1.55 ± 0.14 (mean ± SEM) g/kg per day on day 1 to 1.95 ± 0.15 g/kg per day on day 6 (r = 0.974), followed by a plateau. Two aspects of this curve were critical for subsequent analyses. First, this well-defined relationship between nPCR and day of therapy allowed G_d to be systematically estimated by Equation 2 over the same time period. Knowledge of serial G_d values was required for determination of serial BUN values in the non-steady-state CRRT simulations (Equation 1). Second, the day 6 nPCR value was utilized in both the CRRT and IHD steady-state analyses.

**CRRT Simulations**

For the simulated CRRT regimens, the major input variables were patient dry weight (W_d) and urea clearance (K). In Figure 2, metabolic control data generated for a fixed W_d value (70 kg) and variable K values are shown. Similar sets of curves were generated for all other W_d values. Based on the azotemia curves in Figure 2, several points can be made. First, the contour of these curves is generally representative of the curves generated for other weights. The vast majority of curves demonstrate a relatively steep fall in the BUN over the first 2 days of therapy and a subsequent attainment of steady state at least by day 4. Second, these data corroborate previous reports (1,22) that the typical urea clearance rates achieved by unassisted CAVH (500 to 750 ml/h) result in inadequate azotemia control in hypercatabolic ARF patients of normal or large size (W_d ≥ 70 kg). For a 70-kg patient, the BUN_a predicted for a CRRT urea clearance rate of 750 ml/h is greater than 105 mg/dl. In addition, the azotemia control predicted for a urea clearance rate of 500 ml/h is a continually rising curve over the...
6-day period, ending with a BUN value of approximately 150 mg/dl. This latter curve is one of seven simulated regimens in which a steady-state BUN was not reached by day 6. On the other hand, these data also predict that urea clearance rates easily achieved by CAVHD and venovenous CRRT (≥1000 ml/h) provide steady-state azotemia control at a BUN level of approximately 80 mg/dl or less in patients of normal size. These latter data corroborate clinical experience reported in the literature (7,10,13,16,21).

Data from each simulated CRRT regimen producing a steady-state BUN by day 6 were then used to predict therapy requirements for different clinical scenarios. The first step in this process was to generate a BUNₜ versus K curve for each simulated patient weight. For these curves, a certain desired level of steady-state azotemia control was represented by a horizontal line. The intersection of this horizontal line with the BUNₜ versus K curve for a particular weight produced the value of K required to achieve the chosen level of metabolic control. By applying this same graphical intersection technique to the BUNₜ versus K curves over the entire spectrum of simulated weights, K versus patient weight curves for varying levels of desired azotemia control were produced. These curves, for which the desired BUNₜ targets were 60 (good azotemia control), 80 (moderate azotemia control), or 100 mg/dl (poor azotemia control), are shown in Figure 3.

Over a wide range of patient weights, the data in Figure 3 define ranges of urea clearance required to achieve a certain desired level of metabolic control. For patient weights ranging from 50 to 100 kg, these approximate K ranges are 550 (50 kg) to 1150 (100 kg) ml/h, 650 to 1450 ml/h, and 900 to 1900 ml/h for BUNₜ values of 100, 80, and 60 mg/dl, respectively. Because the venovenous CRRT are able to deliver urea clearance rates of up to 2 l/h in a titratable manner, these data attest to the ability of these therapies to provide excellent azotemia control even in large, hypercatabolic ARF patients.

**IHD Simulations**

The IHD simulations involved the generation of separate BUNₜ versus therapy frequency curves for each patient weight evaluated in the CRRT simulations. For these curves, a certain level of desired time-averaged azotemia control at steady state was represented by a horizontal line. The intersection of this horizontal line with the BUNₜ versus IHD frequency curve for a particular weight produced the treatment frequency required to achieve the chosen level of metabolic control. By applying this same graphical intersection technique to the BUNₜ versus IHD frequency curves over the entire spectrum of simulated weights, IHD frequency versus patient weight curves for varying levels of desired time-averaged azotemia control were produced (Figure 4). These curves, for which the desired BUNₜ targets were the same as the CRRT BUNₜ targets (60, 80, and 100 mg/dl), are based on assumed 4-h dialysis sessions, each achieving a blood urea clearance rate of 180 ml/min. Notably, this latter clearance rate may be close to the maximum achievable value in ARF because of the combination of relatively low blood flow rates and substantial access recirculation and may represent a best-case IHD scenario. Nevertheless, these data predict that an IHD frequency of ≥ five treatments per week in many individuals (weight ≥ 80 kg) still provides only moderate azotemia control (BUNₜ = 80 mg/dl).

An interesting feature of these IHD regimens is the dichotomy between time-averaged and peak azotemia control. Although a relatively infrequent IHD schedule (3.2 times per week) is required for a Wₜ = 50-kg patient to achieve mod-

---

**Figure 3.** Predicted CRRT urea clearance rate required for the attainment of varying desired levels of steady-state azotemia control (BUNₜ). The clearance rates shown are for patients ranging in size from 50 to 100 kg. The target BUNₜ values for curves A, B, and C are 100, 80, and 60 mg/dl, respectively.

**Figure 4.** Predicted IHD frequencies required for the attainment of varying desired levels of time-averaged azotemia control (BUNₜ). The frequencies are shown for patients ranging in size from 50 to 100 kg. The target BUNₜ values for curves A, B, and C are 100, 80, and 60 mg/dl, respectively.
erate time-averaged azotemic control (BUNₐ = 80 mg/dl), this results in a high BUNₐ value (121 mg/dl). On the other hand, the relatively intense IHD regimen (6.2 times per week) required to produce the same BUNₐ value in a 100-kg patient also produces more acceptable peak azotemia control (BUNₚ = 103 mg/dl). Likewise, the relative infrequency of IHD necessary only to achieve poor metabolic control (BUNₐ = 100 mg/dl) results in BUNₚ values that are unacceptably high (range, 127 to 145 mg/dl). Finally, for the attainment of good metabolic control (BUNₐ = 60 mg/dl), the majority of patients require ≥ six dialyses per week. Notably, these data suggest that even a daily 4-h dialysis regimen is not able to provide good azotemia control in patients of body weight > 80 kg.

**Steady-State Therapy Equivalence: CRRT Versus IHD**

In Table 1, steady-state therapy requirement data from both the CRRT and IHD analyses are merged for varying levels of azotemia control. This merging is based on the assumption that a comparison of CRRT BUNₐ and IHD BUNₐ values is most appropriate. Therefore, these BUN values were equated at levels of 60, 80, and 100 mg/dl. This comparison shows that, for individuals as large as 100 kg, both therapies are readily capable of attaining a steady-state BUN value of 100 mg/dl. However, the required treatment intensity differs for the two types of therapies. Even for large (>80 kg) patients, the predicted CRRT clearance rates (approximately 900 ml/h to 1150 ml/h) are at the lower end of clearance rates typically utilized in CAVHD or the venovenous CRRT. On the other hand, although the same steady-state BUNₐ can be achieved with relatively infrequent IHD regimens (<five times per week) in all patients, prolonged interdialytic periods result in high peak BUNₚ values (*vide supra*). The required intensity to achieve good metabolic control (60 mg/dl) differs substantially between the two types of therapies. Over the entire patient weight range, all required CRRT clearance rates are predicted to be less than 2 l/h and therefore would be readily attainable in clinical practice with CAVHD, CVVH, or CVVHD. However, the majority of patients require ≥ six IHD treatments per week for the attainment of a similar BUNₐ value. In addition, this level of metabolic control is not predicted to be possible even with daily dialysis in a number of patients (Wₐ > 80 kg).

**Steady-State Analysis: BUNₐ Versus nPCR/(KT/V)ₐ**

Steady-state RRT azotemia control was expressed as a function of both treatment-related and patient-related parameters by plotting either BUNₐ or BUNₚ versus the ratio nPCR/(KT/V)ₐ. As previously predicted and demonstrated for patients with both ESRD (20) and ARF (21), a linear relationship was observed when these regression analyses were performed. The regression equations produced were as follows: Y = 24.9X - 0.5 (CRRT); and Y = 26.6X + 2.0 (IHD). Although the y-intercepts of both lines approximate 0 as expected, the slope of the IHD line is greater than that of the CRRT line by a factor of 1.07. This factor is essentially a measure of the inefficiency of an intermittent therapy relative to a continuous therapy, as recently discussed (23,24).

To develop this point more fully, the two regression lines for a 70-kg dry weight patient are shown in Figure 5. Because nPCR was constant in these steady-state simulations, variations in the abscissa were entirely the result of changes in (KT/V)ₐ. In turn, changes in therapy dose were related to changes in K for CRRT and in treatment frequency for IHD. Therefore, the points determining the CRRT line represent K values ranging from 750 ml/h (highest nPCR/(KT/V)ₐ value) to 2000 ml/h (lowest nPCR/(KT/V)ₐ value). (A value corresponding to K = 500 ml/h is not shown because this regimen did not produce a steady-state BUN by day 6.) On the other hand, the points on the IHD line represent treatment frequencies ranging from three per week (highest nPCR/(KT/V)ₐ value) to seven per week (lowest nPCR/(KT/V)ₐ value). Figure 5 demonstrates that the degree of divergence between the CRRT BUNₐ and IHD BUNₐ decreases with increasing IHD frequency or de-

**Table 1. Continuous renal replacement therapy clearance rate (ml/h)/intermittent hemodialysis frequency (per week) requirements for varying levels of azotemia control**

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>BUN = 60 mg/dl</th>
<th>BUN = 80 mg/dl</th>
<th>BUN = 100 mg/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>886/4.4</td>
<td>668/3.2</td>
<td>535/&lt;3.0</td>
</tr>
<tr>
<td>60</td>
<td>1097/5.2</td>
<td>823/3.8</td>
<td>649/3.0</td>
</tr>
<tr>
<td>70</td>
<td>1300/6.0</td>
<td>977/4.4</td>
<td>763/3.5</td>
</tr>
<tr>
<td>80</td>
<td>1500/6.9</td>
<td>1123/5.0</td>
<td>886/4.0</td>
</tr>
<tr>
<td>90</td>
<td>1686/NA</td>
<td>1279/5.6</td>
<td>1018/4.5</td>
</tr>
<tr>
<td>100</td>
<td>1911/NA</td>
<td>1432/6.2</td>
<td>1133/5.0</td>
</tr>
</tbody>
</table>

* BUN value is either continuous renal replacement therapy steady-state BUN or intermittent hemodialysis time-averaged BUN. NA, not achievable with daily dialysis.

**Figure 5. Steady-state RRT azotemia control versus the ratio nPCR/(KT/V)ₐ.** The curves are shown for a patient of 70 kg dry weight. The CRRT line represents BUNₐ values, whereas the IHD line represents BUNₐ values.
creasing nPCR/(KT/V)0. This convergence demonstrates that the inherent inefficiency associated with an intermittent therapy, relative to that of a continuous therapy, decreases with increasing frequency of intermittent therapy.

Discussion

Azotemia control and therapy dose are important considerations pertaining to any RRT used for critically ill patients with ARF (3,25,26). With regard to CRRT, the inadequate clearances of low-molecular-weight solutes by CAVH has made its use undesirable, especially for hypercatabolic patients. However, more recently developed CRRT, such as CAVHD, CVVH, and CVVHD, provide improved and more predictable metabolic control. In addition, retrospective data suggest that the higher clearance rates provided by these latter therapies improve ARF patient outcome (8).

In a similar manner, recent preliminary data suggest that the degree of small-solute removal by IHD in critically ill ARF patients influences survival. Tapolyai et al. (27) correlated ICU patient outcome (survival versus nonsurvival) with a variety of clinical and dialytic parameters. Patient demographics, hemodynamic status, and severity scores were all similar in the two groups. Dialysis dose for each treatment was estimated by calculation of KT/V. The prescribed KT/V per treatment was not significantly different between the two groups. However, the mean delivered KT/V per treatment was significantly higher among survivors (survivors, 1.09; nonsurvivors, 0.89).

In a study involving patients treated with both continuous and intermittent therapies, van Bommel et al. (28) recently assessed the possible effect of metabolic control on ARF outcome. These investigators analyzed a series of 94 consecutive ICU ARF patients that were treated with either IHD or CAVHD from 1986 to 1993. The typical IHD blood flow rate and dialysis duration were 150 to 175 ml/min and 4 h per treatment, respectively, whereas the mean frequency of dialysis was approximately once every 2 days. Reflective of practices at many centers, patients with greater illness severity tended to be treated with CRRT rather than IHD. Based on the APACHE II scoring system (29), the predicted risk of death was significantly higher for the CAVHD group than for the IHD group. With regard to solute control, the initial BUN was significantly higher in the CAVHD than in the IHD group (135 versus 105 mg/dl, respectively). However, although the mean CAVHD BUN fell to 85 mg/dl by day 6, the daily BUN in the IHD group, time-averaged for the peak and trough effect of dialysis, remained essentially unchanged and significantly higher than the corresponding CAVHD value. Despite the greater acuity of illness and higher predicted risk of death in the CAVHD patients, their mean survival was not significantly different from that in the IHD group. These data suggest that the superior metabolic control provided by CAVHD, relative to a standard IHD regimen, may have played a role in providing a relative survival advantage.

The data of van Bommel et al., along with other clinical assessments of metabolic control by CRRT and IHD (21,30), provide confirmation of our present theoretical investigation. Our simulated analyses predicted that conventional administra-
the CRRT line by a factor of 1.07. Therefore, for the same treatment dose, \((KT/V)_d\), the IHD \(BUN_p\) value exceeded the CRRT \(BUN_p\) value by this same factor. This factor essentially quantifies the inefficiency of an intermittent therapy relative to a continuous therapy, an issue that has been the subject of debate in the ESRD arena (23,34). Our analysis also showed that because the \(y\)-intercepts of these regression lines both approximated zero, the lines converged with increasing IHD frequency (Figure 5). Therefore, increasing IHD frequency resulted in metabolic control that began to approximate that achieved by a continuous therapy. Finally, although we chose to utilize CRRT \(BUN_p\) and IHD \(BUN_p\) values in our comparative analysis, previous investigations involving both ESRD (34,35) and ARF (21) patients have suggested that the use of peak IHD azotemia control is more appropriate. In an analysis comparing outcome of ESRD patients treated with either hemodialysis or CAPD, Keshaviah et al. (35) recently presented preliminary data that support this hypothesis. The most appropriate comparative method for intermittent and continuous therapies in the ARF and ESRD settings will only be resolved definitively by prospective studies.

Because we utilize CVVH at our institution, urea clearance was equated with UFR for the purpose of this investigation. However, use of our predictive model is not limited to purely convective CRRT. The CRRT urea clearance rates predicted by our model (Figures 2 and 3, Table 1) are total urea clearance rates required to achieve a certain level of desired azotemia control. Therefore, the model is also adaptable for use with other CRRT, such as CVVHD and CAVHD, in which the total urea clearance rate is comprised of both convective and diffusive components and approximates the dialysate outflow rate. This adaptation is possible because of the existence of dialysis equilibrium in these latter therapies (11,13).

Certain assumptions made in the development of the model may represent limitations of this investigation. One potential weakness is our assumption that the convective clearance of urea and UFR were the same. For predilutional hemofiltration, the UFR represents a maximally achievable value of solute clearance (36). We also assumed that the urea sieving coefficient for the hemofilters was 1.0 during their entire duration of use, which was limited to 48 h or less. Golper et al. (37) demonstrated that hemofilter sieving coefficients remain very close to 1.0 during filter lives of similar duration. The above two assumptions may have resulted in a slight \((\leq 5\%)\) overestimation of urea nitrogen clearance rates. This degree of error is satisfactory for a model that is designed only to predict approximate rather than specific therapy requirements. Our finding of a linear relationship between the nPCR and CVVH treatment duration during the non-steady-state CRRT simulations and the use of a fixed (day 6) nPCR value for the steady-state CRRT and IHD determinations are also potential limitations of the study. Both the linear non-steady-state relationship between nPCR and day of therapy and the attainment of a steady-state nPCR are in contrast to the work of Chima et al. (38), who reported that nPCR is related to treatment duration in a random manner for patients receiving CAVH. Thus, the extrapolation of our nPCR standard curve to other patient populations with ARF may be problematic. However, at least four recent investigations involving ARF patients treated with both CRRT (15,21,38) and IHD (39) have reported mean nPCR values in the same range (1.55 to 1.95 g/kg per day) that we observed. The urea distribution volume (\(V\)) range over which our simulations were performed may prevent extrapolation to some patient groups, representing another potential limitation. Based on our previous analysis of a group of CVVH patients at steady state (16), we chose a \(V\) equal to approximately 0.56 l/kg for the euvolemic (steady-state) value. This closely approximates euvolemic values in both the healthy (40,41) and ESRD (20) patient populations. However, we (3,42) have recently shown that the treatment of volume overload in ARF patients even over a prolonged period of IHD may not result in fractional urea distribution volumes consistent with euvolemia. This analysis showed that the mean fractional value of \(V\) was 0.65 l/kg in a group of 11 ARF patients who received prolonged courses of IHD. It also demonstrated that the elevated fractional TBW in ARF patients adversely affects azotemia control relative to that which would be attained with similar amounts of therapy delivered to patients with near-normal fractional TBW. These findings must be considered when this model is applied to patients with severe, refractory volume overload.

A constraint of the analysis presented here, not related to the model itself, is the general use of clearance-based methods for quantification of small-solute removal. The relative inefficiency of IHD relates to the decreasing mass removal rate of small solutes with increasing treatment time despite a constant clearance. On the other hand, mass removal rate in a CRRT is directly proportional to clearance. Although we have attempted to account for this difference, the optimal solution to this problem may be the use of dialysate-based quantification methods utilized in ESRD patients (43). These latter techniques avoid the pitfalls of clearance-based methods in their ability to quantify urea mass removal directly. Finally, the analysis presented here does not account for the significant differences between IHD and CRRT in the removal profiles of solutes other than urea. The relative importance of convection and treatment time on solute removal increases with increasing solute size (44,45). Therefore, particularly for continuous modalities using high ultrafiltration rates, middle-molecule and low-molecular-weight protein removal by CRRT is superior to that of IHD. Whether or not this superiority affords a clinical advantage has not been determined.

In conclusion, we have presented a computer-based model, based on actual patient data, designed to predict extracorporeal therapy requirements in critically ill ARF patients. This model is applicable to IHD and all CRRT and has been corroborated by retrospective clinical data (21,28). The model suggests that for many patients, relatively strict azotemia control equivalent to that readily attainable with most CRRT can only be achieved with intensive IHD regimens. In this respect, superior azotemia control appears to be another advantage of CRRT over IHD in the management of critically ill ARF patients. Finally, this study quantifies the difference in efficiencies between inter-
mitten and continuous therapies in ARF. In this respect, our results may also have utility in the dialytic management of ESRD patients (23,34,35).

References


