Dose of Dialysis Based on Body Surface Area Is Markedly Less in Younger Children Than in Older Adolescents

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Background and observations: The current denominator for dosing dialysis is the urea distribution volume (V). Normalizing Kt/V to body surface area (S) has been proposed, but the implications of doing this in children have not been examined.

Design, setting, participants, & measurements: Dialysis dose given to children and adolescents was calculated in terms of conventional V-based scaling and surface-area-normalized standard Kt/V (SAN-stdKt/V) calculated as stdKt/V/(Vant/S)/17.5, where Vant was an anthropometric estimate of V calculated using the Morgenstern equation. Formal 2-pool modeling was used to compute all dialysis adequacy outputs.

Results: In 34 children (11 girls, 23 boys) dialyzed 3 times a week, age range 1.4 to 18 years, the mean delivered equilibrated Kt/V (eKt/V) was 1.40, and the mean stdKt/V was 2.49, both of which tended to be higher in younger children. The ratio of Vant to S was 15.6 ± 2.69 and was strongly associated with age between ages 2 and 16. SAN-stdKt/V averaged 2.21 and was strongly correlated with age between ages 2 and 16. If one considers a desired target for SAN-stdKt/V to be 2.45, all children less than 10 years of age were below target, despite having relatively high values of eKt/V and stdKt/V.

Conclusions: If a surface-area-based denominator were to be adopted for dialysis dosing, most children under 10 years of age would receive markedly less dialysis than adolescent patients and would require 6- to 8-hour hemodialysis sessions or, for the youngest children, treatments given more frequently than 3 times/wk.


The minimum hemodialysis dose needed by adults and children is a matter of some uncertainty and considerable controversy. When dose is scaled to urea distribution volume (V), which is similar in size to total body water, and when hemodialysis is given 3 times/wk, observational data suggest that the minimum per-session dose in adults is a Kt/V of 1.2, where K is the dialyzer clearance and t is the dialysis session length (1). The dose of dialysis can also be expressed as a weekly equivalent, standard Kt/V (2–4). Standard Kt/V (stdKt/V) is calculated as the urea generation rate (G) divided by the mean predialysis urea concentration multiplied by 10,080 (the number of minutes in a week) and divided by V. When stdKt/V is estimated by a fixed-volume, simplified equation (4), a value of 2.0 corresponds to a session Kt/V of 1.2 in a thrice-weekly schedule (1). When formal modeling is used to compute the stdKt/V, the corresponding value is somewhat higher, approximately 2.14, because of the effects of fluid removal (5).

Current Kidney Disease Outcomes Quality Initiative (K/DOQI) recommendations for a 3-times/wk schedule of dialysis are to keep the single-pool Kt/V (spKt/V) >1.2, or the stdKt/V (estimated by a fixed-volume, simplified equation) at >2.0 (1). In adults, providing a larger amount of dialysis while still keeping to a 3- to 4.5-hour, 3-times/wk schedule appears to be of little benefit, as shown by the Hemodialysis (HEMO) study in which patients randomized to “high-dose” dialysis (an spKt/V of approximately 1.7) had mortality and hospitalization rates similar to patients randomized to “conventional-dose” dialysis (an spKt/V of approximately 1.3) (6). The stdKt/V values in these two groups, calculated using formal modeling, were 2.62 and 2.24, respectively (7). In adults, current research is focusing on whether further increases in the stdKt/V, to approximately 4.0 using a 6-times/wk “daily” schedule (150-minute sessions) or to approximately 6.0 using a 6-times/wk nocturnal schedule (400-minute sessions), might be of benefit in terms of intermediate outcomes (8).

In children on maintenance hemodialysis, there is scant observational evidence and no randomized trials regarding the optimum dose of dialysis. Given the relatively robust amount of protein ingestion in children and the belief that inadequate dialysis can impair somatic growth, the current concept is that children require relatively more dialysis than adults, although the amount of increase is unclear. The current K/DOQI guidelines (8.3.1 and 8.3.2 in reference 1) state that “children should receive at least the delivered dose of dialysis as recommended for the adult population” (level A evidence) and that “for younger pediatric patients, prescription of higher dialysis doses and higher protein intakes at 150% of the recommended nutrient intake for age may be important” (level B evidence). In the United States, according to 2005 U.S. Renal Data System
and to determine what would constitute a dose equivalent to the effect of rescaling dialysis dose to S in children of different ages. The purpose of the study presented here was to examine the size, rescaling dialysis dose to S rather than to V will result in a V to S ratio that is higher in men than in women, and because the ratio of S to body size, rescaling dialysis dose to S rather than to V will result in a requirement for a relatively greater amount of dialysis for women and for smaller patients, including children (7,15–18). The purpose of the study presented here was to examine the effect of rescaling dialysis dose to S in children of different ages and to determine what would constitute a dose equivalent to that currently given to older adolescents and to adults.

Patients and Methods

Monthly modeling sessions from one pediatric dialysis unit in Jerusalem, Israel (center 1), and one in Chicago, Illinois (center 2), were used as the basis of this analysis. All patients used for analysis were being dialyzed 3 times/wk (a few patients were being dialyzed ≥3 times/wk, but these were excluded). Selected patient characteristics are given in Table 1; the causes of end-stage kidney disease were typical of what is seen in childhood. In center 1, causes of ESRD were dysplastic kidneys (5), atypical hemolytic uremic syndrome (3), posterior urethral valve (1), focal segmental glomerular sclerosis (1), familial nephrotic syndrome (3, with 1 podocin mutation, others negative for known mutations), and sepsis-ischemia (1). In center 2, causes of ESRD were unknown (7), reflux nephropathy (3), lupus (2), IgA (1), membrane proliferative GN type I (1), Wegener’s (1), focal segmental glomerular sclerosis (1), HIV (1), cystinosis (1), and cloacal extrophy (1). Children dialyzed in center 1 were considerably younger than those being dialyzed in center 2. None of the patients in center 1, with the exception of the youngest (1.4 years of age), had any urine output. In center 2, several children had small amounts of residual renal function. In center 1, 9 of 14 patients were using catheters, 5 of 14 an AV fistula, and none were using a graft. In center 2, the proportions were 13 of 20, 7 of 20, and 1 of 20, respectively.

Anthropometric total body water volume was estimated from height, weight, age, and gender using equations by Morgenstern (19) for all patients. S was calculated using the equation of Gehan and George (20). Formal urea modeling was used to compute adequacy values in these children. The details of the model used (Solute–Solver) have been described in detail (21). Briefly, the model uses a 2-pool, variable extracellular volume analysis in which K is computed from industry-published KpA values and recorded blood and dialysate flow rates. The model assumes that patients are dialyzed to the same postdialysis weight throughout the week and uses numerical integration of urea concentrations in the two body pools to generate a weekly blood urea nitrogen (BUN) profile. The intercompartmental mass transfer clearance for urea is estimated as 16 × the postdialysis volume in liters (21).

The surface-area-normalized (SAN) stdKt/V is computed as stdKt/V multiplied by (Vant/S, where Vant is the anthropometric estimation of body water) divided by the population mean of the Vant-to-S ratio, as described previously (7,17). The latter normalizing number will vary depending on how V is measured. In adults, when the Vant-to-S ratio is estimated using the equations described by Watson et al. for Vant (22) and Dubois and Dubois for S (23), the population mean value of Vant/S is close to 20 (17). In children, when the Morgenstern equation (19) is used for Vant and the Gehan and George equation is used for S (20), the population mean value for Vant/S (Morgenstern/Gehan) in older adolescent children is close to 17.5, and this was the normalization value used to compute SAN-stdKt/V in the data analysis presented here.

Treatment characteristics for the children in the two centers are given in Table 2. In center 1, all of the patients were receiving hemodialysis for 4 hours, 3 times/wk, whereas in center 2 the treatment time was variable, averaging 214 minutes. Mean dialyzer KpA and estimated Kd values are as shown. The average blood flow was 124 ml/min in center 1 and 246 ml/min in center 2. Dialysate flow rate was fixed at 500 ml/min in both centers.

### Table 1. Patient characteristics

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</tr>
<tr>
<td>Gender (male/female)</td>
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<td>12/8</td>
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<td>Age (years)</td>
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<td>Height (cm)</td>
<td>104 ± 27</td>
<td>150 ± 18.9</td>
<td>131 ± 31.8</td>
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<tr>
<td>Weight (kg)</td>
<td>18.9 ± 11</td>
<td>46.6 ± 16.5</td>
<td>35.2 ± 20.0</td>
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<td>S (m²)</td>
<td>0.75 ± 0.31</td>
<td>1.39 ± 0.33</td>
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<td>Vant (L)</td>
<td>10.9 ± 6.44</td>
<td>24.5 ± 6.86</td>
<td>18.9 ± 9.47</td>
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Table 2. Treatment characteristics

<table>
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<th>Center 2</th>
<th>All</th>
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</thead>
<tbody>
<tr>
<td>Qb (ml/min)</td>
<td>124 ± 65</td>
<td>246 ± 75.0</td>
<td>195 ± 92.9</td>
</tr>
<tr>
<td>Qb/S (mL/min⁻¹m⁻²)</td>
<td>160 ± 29</td>
<td>178 ± 32</td>
<td>170 ± 32</td>
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<tr>
<td>Qd (ml/min)</td>
<td>500 ± 0</td>
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<td>500 ± 0</td>
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<td>Qd/Qb (ratio)</td>
<td>5.11 ± 2.34</td>
<td>2.2 ± 0.68</td>
<td>3.41 ± 2.12</td>
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<td>KcA (ml/min)</td>
<td>494 ± 175</td>
<td>967 ± 328</td>
<td>772 ± 360</td>
</tr>
<tr>
<td>Kd (ml/min)</td>
<td>92.9 ± 43</td>
<td>177 ± 47.8</td>
<td>142.6 ± 62</td>
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<tr>
<td>t (minutes)</td>
<td>240 ± 0</td>
<td>214 ± 23.7</td>
<td>225 ± 22</td>
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</table>

Qb, blood flow rate; Qd, dialysate flow rate; KcA, dialyzer mass transfer area coefficient; Kd, dialyzer clearance; t, dialysis time.

Results

The single- and double-pool modeling outputs are given in Table 3. The mean urea reduction ratio (URR) and spKt/V were 72.8 and 1.60, respectively, and the mean equilibrated Kt/V (eKt/V) was 1.40. StdKt/V averaged 2.49, well above the K/DOQI-recommended minimum value of 2.14 (after factoring in fluid removal). The mean modeled volume (Vm, 20.8 L) was similar to Vant (18.9 L; Table 1), with an average Vm-to-Vant ratio of 1.13. The ratio of Vm to S in older adolescents was slightly higher in the younger children. Figure 3 shows that the Vant-to-S ratio was considerably lower than the mean value of approximately 17.5 seen in older adolescents (Figure 3). In Figure 3, the Vant-to-S ratio is normalized to the mean value found in older adolescents of approximately 15.6, with a strong relationship to age. The SAN-stdKt/V averaged 2.21.

The relationships of eKt/V, stdKt/V, Vant/S, and SAN-stdKt/V to age are shown in Figures 1 through 5. From Figures 1 and 2, it is clear that eKt/V and stdKt/V values tended to be slightly higher in the younger children. Figure 3 shows that the Vant-to-S ratio fell progressively as children were younger, and that at ages 2 to 5 the Vant-to-S ratio was considerably lower than the mean value of approximately 17.5 seen in older adolescents (Figure 3). In Figure 3, the Vant-to-S ratio is normalized to the mean value found in older adolescents of approximately 17.5, and the data are displayed in percent format. Figure 4 shows that a similar relationship of V/S was present when Vm was used. The average ratio of Vm to S in older adolescents was close to 20 (19.8). Hence, in Figure 4 the Vm-to-S ratio is expressed as a percent of 20.

We considered that a reasonable target (not necessarily a minimum value) for SAN-stdKt/V would be 2.45 as measured by formal modeling because this was the mean value seen in the women randomized to the high-dose group in the HEMO study and was the value seen in the men randomized to the conventional-dose group (7). Figure 5 shows the values of SAN-stdKt/V in our patients as a function of center, gender, and age. SAN-stdKt/V was progressively lower in the children younger than age 14 and was lower than the candidate target value of 2.45 in all children <12 years of age regardless of gender.

To determine the dialysis prescription that would be required in the children <14 years of age to achieve a SAN-stdKt/V value of 2.45, we simulated weekly BUN profiles for each of the children in center 1 using the same K and fluid removal rate and the same value for V and G as calculated in their modeling session. We increased time progressively, keeping to a 3-times/wk schedule, to a maximum time value of 8 hours. The results are presented in Table 4. The three patients from center 1 who were 12 to 13 years of age were already close to a hypothetical SAN-stdKt/V target of 2.45 and would need only minimal, if any, changes to their existing prescriptions. Three patients aged 7.5 to 10 years would need to have session lengths extended to 5 to 6 hours to achieve a 2.45-SAN-stdKt/V target using a thrice-weekly schedule, although perhaps some

Table 3. Modeling outputs

<table>
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<th>Center 1</th>
<th>Center 2</th>
<th>All</th>
</tr>
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<tbody>
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<td>URR</td>
<td>77.3 ± 3.75</td>
<td>69.7 ± 5.63</td>
<td>72.8 ± 6.21</td>
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<tr>
<td>spKt/V</td>
<td>1.81 ± 0.18</td>
<td>1.45 ± 0.23</td>
<td>1.60 ± 0.28</td>
</tr>
<tr>
<td>eKt/V</td>
<td>1.61 ± 0.16</td>
<td>1.26 ± 0.21</td>
<td>1.41 ± 0.26</td>
</tr>
<tr>
<td>G (mg/min)</td>
<td>2.88 ± 1.36</td>
<td>4.86 ± 2.05</td>
<td>4.05 ± 2.03</td>
</tr>
<tr>
<td>PCRn (g/kg/day)</td>
<td>1.53 ± 0.50</td>
<td>1.14 ± 0.25</td>
<td>1.30 ± 0.42</td>
</tr>
<tr>
<td>stdKt/V (dialysis)</td>
<td>2.70 ± 0.13</td>
<td>2.34 ± 0.34</td>
<td>2.49 ± 0.27</td>
</tr>
<tr>
<td>SAN-stdKt/V (dialysis)</td>
<td>2.12 ± 0.38</td>
<td>2.28 ± 0.29</td>
<td>2.21 ± 0.48</td>
</tr>
<tr>
<td>Vm (L)</td>
<td>11.87 ± 5.46</td>
<td>27.0 ± 9.19</td>
<td>20.8 ± 10.9</td>
</tr>
<tr>
<td>Vm/Vant</td>
<td>1.14 ± 0.18</td>
<td>1.11 ± 0.16</td>
<td>1.13 ± 0.17</td>
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<tr>
<td>Kc (ml/min)</td>
<td>187 ± 88</td>
<td>433 ± 147</td>
<td>333 ± 173</td>
</tr>
<tr>
<td>Vant/S</td>
<td>13.7 ± 2.30</td>
<td>17.0 ± 1.17</td>
<td>15.6 ± 2.69</td>
</tr>
</tbody>
</table>

PCRn, normalized protein catabolic rate; Vm, modeled urea volume; Vant, anthropometric urea volume; Kc, intercompartmental urea clearance.
additional increase in blood flow or dialyzer efficiency might allow a slightly shorter session length. The required 5- to 6-hour session lengths would not be practical unless a nocturnal dialysis schedule were to be adopted. Otherwise, these three patients would need to dialyze more frequently than thrice weekly. The remaining seven patients from center 1 were ≤5 years of age. In four of these seven, a SAN-stdKt/V target of 2.45 could be achieved using a 3-times/wk schedule, but only if t was extended to 8 hours, perhaps using a nocturnal schedule. In the remaining three of these youngest patients, dialysis would have to be given more frequently than 3 times/wk.

**Discussion**

In these two pediatric dialysis units, children were being dialyzed 3 times/wk and their delivered dialysis dose, as assessed by formal modeling, was completely compliant with current K/DOQI guidelines (1). In center 1 and 2, respectively, the mean URR values were 77% and 70%, the spKt/V values averaged 1.81 and 1.45, and the stdKt/V values averaged 2.70 and 2.34. These values are well above the K/DOQI recommended minimums for adults and children of 65% (URR), 1.2 (spKt/V), and 2.14 (stdKt/V when measured by formal mod-
elings). However, on rescaling dose to S, specifically, in terms of Vant/S-normalized stdKt/V, the dialysis dose received by these children, especially those <10 years of age, was much less than comparable SAN doses being given to older adolescents. In children <7 years of age, the shortfall in dose was of such a magnitude that, to correct it, a change to a more frequent dialysis schedule would most likely be necessary.

What is the rationale for changing the dialysis denominator from V to S? The concept of using V is based on the use of urea as a target solute. Urea is distributed in the total body water, and GFR is proportional to V (12). However, total body water in adult patients is importantly determined by muscle mass. It is not clear that muscle tissue per se generates important amounts of uremic toxins (18). Also, the amount of muscle mass relative to S is higher in men than in women and higher in African Americans than in Caucasians (reviewed in reference 18). Adjusting dialysis dose on the basis of V is a de facto adjustment of dialysis dose to muscle mass, and a V-based dosing system will result in relatively more dialysis for men than comparably sized (in terms of S) women and more dialysis for African Americans than for comparably sized Caucasians (7, 15–18). Also, because V is more steeply related to body weight than is S, a V-based dialysis dosing system will allow marked reductions in dose for lighter patients compared with heavier patients, more so than an S-based dosing system, because the decrement in S for lighter patients is relatively attenuated compared with the decrement in V (7, 15–18).

In effect, if one considers dialysis as “replacement renal function,” it makes some sense to scale dialysis to body size and age the same way the kidney function calculated as GFR is scaled. In adult kidney donors, iothalamate-measured GFR is higher in men than in women, but the difference disappears when GFR is scaled to S (24). In contrast, if GFR is scaled to V, a marked gender disparity results, with adjusted GFR/V being considerably higher in women than in men (24). In children, inulin-measured GFR divided by S is relatively constant in different age groups until one gets below 2 years of age (reviewed in reference 25). Kidney size, which logically is related to GFR, also is related to S (reviewed in reference 25).

Whereas the argument of scaling dialysis dose to V or S in adults affects primarily sex-based differences, in prepubertal children especially the ratio of V to S in both genders is markedly lower than that in older adolescents or adults. For example, in adult ESRD patients enrolled in the HEMO study, the median ratio of Watson-estimated V to Dubois-estimated S was approximately 18.5 in women and 21.5 in men (17). For this reason, a value of 20 for the Vant-to-S ratio represents more or less a population mean value for adult (late middle-age or elderly) ESRD patients. In the data presented here, in adolescents aged 15 to 18, Vant/S calculated using Morgenstern/Gehan averaged approximately 17.5, considerably lower than the mean value of 20 using Watson/Dubois in HEMO study patients. However, the Watson estimate was derived from healthy subjects, and when we calculated the population mean V-to-S ratio using an estimating equation for V developed using the HEMO study data (26), this ratio was also in the range of 17.5 to 18 (7). The actual value of the mean V-to-S ratio is not critical. The SAN-stdKt/V normalization adjusts to whatever the mean value is in adults to allow for compensation for the effects on the V/S ratio of gender (in adults) or age in younger children.

Figures 3 and 4 show what the percent difference in dose will be when comparing a V-scaled dialysis measure with an S-scaled measure. It can be seen from these figures that a 10-year-old child will have a V-to-S ratio that is approximately 80% that of an older adolescent, and a 4-year-old child will have a V-to-S ratio that is approximately 60% to 70% of the older adolescent value. Therefore, their required dialysis doses would need to be multiplied by 1/0.8 = 1.25, or 1/0.65 = 1.53, respectively. Ideally this adjustment should be applied to a continuous equivalent of the dialysis dose (e.g., stdKt/V). For any given frequency of treatments per week, the relationship between session eKt/V and stdKt/V is curvilinear; hence, it is difficult if not impossible to achieve a 50%, or even a 25%, increase in stdKt/V unless the frequency of treatments is increased.

In our simulations, we chose a target SAN-stdKt/V of 2.45. This is the value that was attained in the women randomized to the high-dose group in the HEMO study (URR of approximately 75%). However, this is also close to the currently prescribed dose for women as shown by the fact that in recent USRDS data reports, the mean URR in women is currently approximately 75% (27) The SAN-stdKt/V value of 2.45 corresponds to a URR of only 67% in men in the HEMO trial, and this is actually lower than the URR currently being delivered according to information from the 2009 USRDS data (27).

Although there are no randomized trials of dialysis adequacy in children, there are several observational studies reporting improved results with more frequent dialysis (reviewed in reference 28). Two recently reported series are of interest: one by Tom et al. (10), in which 5-hour, 3-times/wk treatments were given; and one by Fischbach et al. (11), in which 3-hour, 6-times/wk hemodiafiltration treatments were provided. In

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Figure 5. SAN-stdKt/V versus age. A proposed target SAN-stdKt/V value of 2.45 is also shown.
both series, a marked increase in growth was reported. Using
the data from the patients reported in these papers, we com-
puted the approximate dose in terms of the SAN-stdKt/V that
was being delivered. The Vant-to-S ratio in this calculation was
not done on a per-patient basis because height and weight were
not available, but we used the general regression of Vant/S
versus age derived from Figure 3. The results are shown in
Figure 6. It is clear that in the 3-times/wk treatments given by
Tom et al. (10), SAN-stdKt/V values of 2.45 were achieved in the
older children, although not in those under age 10. In the
Fischbach study, all children had SAN-stdKt/V values well
over 2.45. Also, in the latter treatment group, the provision of
convective solute removal via hemodiafiltration may have
been of additional benefit.

We believe it would be premature to suggest mandating a
change to more frequent dialysis in younger children at this
point in time. Such a change in clinical practice would have
major implications: Should all pediatric dialysis centers now
present dialysis as a 4- to 6-d/wk therapy for all patients
younger than 10 to 12 years of age? This would have substantial
financial ramifications as well as other issues—social, educa-
tional, organizing the family around the child’s care, etc. One
must be careful about recommending a global increase in pe-
diatric dialysis dose on the basis of a theoretical analysis, and
further studies, including randomized controlled trials with
hard end points, are urgently needed in this area.

If one did move to a more frequent dialysis schedule, attain-
ment of a SAN-stdKt/V of 2.45 would be very easy, even for
very young patients with a low Vant-to-S ratio. For example,
two very young patients in center 1 are on 6-d/wk dialysis
to achieve maximum clearance of oxalate. Their SAN-std Kt/V
values (3.36 and 4) were well above 2.45, despite an S value of
only 0.5 m² and Vant/S of approximately 11.

In summary, our results suggest that if one rescales dialysis
dose proportional to S, then most children <10 years of age
being dialyzed 3 times a week are not currently achieving a
SAN dose comparable to those given routinely to adult patients
or to older adolescents. This is true even when levels of session
eKt/V are quite high and t is 4 hours. To achieve such a
comparable SAN dose, most children <10 years of age would
require hemodialysis >3 times/wk.

Disclosures

None.

Table 4. Target stdKt/V values and projected stdKt/V with increasing t for patients in Center 1 with age <14 years

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<thead>
<tr>
<th>Age (years)</th>
<th>Vant/S</th>
<th>Actual stdKt/V (t = 240 minutes)</th>
<th>Target stdKt/V&lt;sup&gt;a&lt;/sup&gt; (SAN-stdKt/V = 2.45)</th>
<th>Projected stdKt/V at t (minutes)</th>
<th>Target t (minutes)</th>
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<tbody>
<tr>
<td>1.4</td>
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<td>2</td>
<td>11.8</td>
<td>2.87</td>
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<td>2.63</td>
<td>3.60</td>
<td>2.94 3.18 3.38</td>
<td>&gt;480</td>
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<td>2.69 2.93 3.13</td>
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<td>2.99 3.20 3.36</td>
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<td>5</td>
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<td>2.60</td>
<td>2.86</td>
<td>2.88 3.10 3.27</td>
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</table>

<sup>a</sup>Target stdKt/V calculated as 2.45×Vant/S.

Figure 6. Estimated SAN-stdKt/V versus age in two studies in which increased growth rates were linked to intensified dialysis
regimens, one with hemodialysis treatments given 3 times/wk
by Tom et al. (10) and one using 6-times/wk hemodiafiltration
by Fischbach et al. (11).
References


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