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## DAILY HEMODIALYSIS AND THE OUTCOME OF ACUTE RENAL FAILURE

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### ABSTRACT

**Background** Intermittent hemodialysis is widely used as renal-replacement therapy in patients with acute renal failure, but an adequate dose has not been defined. We performed a prospective study to determine the effect of daily intermittent hemodialysis, as compared with conventional (alternate-day) intermittent hemodialysis, on survival among patients with acute renal failure.

**Methods** A total of 160 patients with acute renal failure were assigned to receive daily or conventional intermittent hemodialysis. Survival was the primary end point of the study. The duration of acute renal failure and the frequency of therapy-related complications were secondary end points.

**Results** The two study groups were similar with respect to age, sex, cause and severity of acute renal failure, medical or surgical intensive care setting, and the score on the Acute Physiology, Age, and Chronic Health Evaluation. Daily hemodialysis resulted in better control of uremia, fewer hypotensive episodes during hemodialysis, and more rapid resolution of acute renal failure (mean [ $\pm$ SD],  $9\pm 2$  vs.  $16\pm 6$  days;  $P=0.001$ ) than did conventional hemodialysis. The mortality rate, according to the intention-to-treat analysis, was 28 percent for daily dialysis and 46 percent for alternate-day dialysis ( $P=0.01$ ). In a multiple regression analysis, less frequent hemodialysis (on alternate days, as opposed to daily) was an independent risk factor for death.

**Conclusions** The high mortality rate among critically ill patients with acute renal failure who require renal-replacement therapy is related to both coexisting conditions and uremic damage to other organ systems. Intensive hemodialysis reduces mortality without increasing hemodynamically induced morbidity. (N Engl J Med 2002;346:305-10.)

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THE high mortality rate among critically ill patients with acute renal failure remains an unsolved problem in intensive care medicine, despite the fact that renal-replacement therapy has been available for decades. Many such patients have preexisting conditions that predispose them to acute renal failure and to concomitant extrarenal complications that cause multiorgan failure.<sup>1,2</sup> However, renal failure and its associated metabolic alterations also appear to increase the risk of severe extrarenal complications, which are often fatal.<sup>3,4</sup>

Although there is a consensus that the delivered dose of maintenance hemodialysis is inversely related to morbidity and mortality, there is no consensus on the appropriate dose in patients with acute renal failure. The current practice of determining the dose is based on an early prospective study by Gillum et al.,<sup>5</sup> who compared daily and alternate-day hemodialysis in 17 matched pairs of patients with acute renal failure due to medical conditions, surgery, or trauma. The patients who received the higher dose were less likely to have gastrointestinal bleeding and septicemia than were the patients who received the lower dose, but there was a trend toward higher mortality in the high-dose group (seven of nine patients died [77.8 percent] in the subgroup with renal failure due to surgery or trauma, as compared with five of nine such patients who received nonintensive dialysis [55.6 percent]).<sup>5</sup> In contrast, an analysis of retrospective data from the Cleveland Clinic Foundation registry suggested that the patients with acute renal failure in the intensive care setting who survived had received a higher dose of hemodialysis than those who had died.<sup>6</sup> The authors found that the delivered dose, calculated according to urea kinetics, was actually lower than the prescribed dose.<sup>6</sup>

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Ronco et al.<sup>7</sup> conducted a large, prospective study of the effects of different ultrafiltration volumes in patients with acute renal failure who were treated with continuous venovenous hemofiltration. The investigators found that higher prescribed volumes were associated with reduced mortality rates. The hypothesis that increasing the intensity of the delivered dose of hemodialysis in critically ill patients with acute renal failure reduces the rate of uremic complications and improves the outcome is logical yet remains unproved, since it is based on scarce and conflicting data.

We conducted a prospective study to compare the effect of daily intermittent hemodialysis with alternate-day hemodialysis on survival among patients receiving intensive care for acute renal failure.

## METHODS

The study population comprised adults with acute renal failure in the medical and surgical intensive care units at the University Hospitals of Munich, Innenstadt, Germany. The main criterion for inclusion in the study was a clinical diagnosis of severe acute tubular necrosis caused by a recent ischemic or nephrotoxic injury, with an anticipated need for intermittent hemodialysis for at least one week. Severe acute tubular necrosis was defined as a rapidly rising serum creatinine level (an increase of at least 1 mg per deciliter [88.4 mmol per liter] per day) or marked azotemia (serum creatinine,  $\geq 4$  mg per deciliter [353.6 mmol per liter]) and a history of prolonged and profound hypotension, a severe overdose of nephrotoxins and the presence of risk factors for nephrotoxic acute tubular necrosis, or an excessive body burden of endogenous nephrotoxic pigments (myoglobin and hemoglobin). The diagnosis was based on the clinical history; the results of the physical examination, relevant blood tests, and urinalysis (microscopical examination of urinary sediment); a fractional excretion of sodium that exceeded 2 percent; and the findings on renal ultrasonography and duplex ultrasonography. Patients were excluded from the study if they had any of the following: functional azotemia; urinary tract obstruction; acute interstitial nephritis; rapidly progressive glomerulonephritis; a history of chronic renal insufficiency (serum creatinine  $> 3$  mg per deciliter [265.2 mmol per liter]), renal transplantation, or hemodialytic or filtrative therapy for the same episode of acute renal failure; or an indication for continuous renal-replacement therapy (hepatorenal syndrome or cardiogenic shock). The study protocol was approved by the institutional review board. Written informed consent was obtained from all the study participants or from their next of kin.

### Criteria for Hemodialysis

Attending nephrologists in the intensive care units selected patients for enrollment and decided when to prescribe hemodialysis and when to terminate it. We were consulted about these decisions for only 6 of the 160 enrolled patients. The indications for hemodialysis were volume overload, electrolyte imbalance, uremic symptoms, acid-base disturbances, and a blood urea nitrogen level that exceeded, in some cases, 100 mg per deciliter (35.7 mmol per liter). These conditions were unresponsive to medical management. Hemodialysis was terminated when there was partial recovery of renal function, defined as the restoration of diuresis, the absence of uremia, and improved electrolyte and acid-base homeostasis.

### Treatment Assignments

Consecutively enrolled patients were assigned in alternating order to receive daily or conventional hemodialysis. To minimize bias in the selection of patients, a number of precautions were taken.

Once the attending nephrologist had recommended hemodialysis for a patient and the patient's eligibility for enrollment had been verified, the treatment was assigned by the investigators without knowledge of the identity of the individual patient or of the clinical characteristics that were predictors of the outcome. The treatment was performed by separate teams of nephrologists, who were working in the intensive care units on a clinical rotation over a period of nearly six years. These physicians, as well as the patients and the nursing staff, were unaware of the treatment assignments until the first session of hemodialysis had been completed. After the first session, no attempts were made to maintain the blinded conditions.

Hemodialysis was performed with volumetrically controlled machines (MTS 2008C, Fresenius, Bad Homburg, Germany) and the use of bicarbonate dialysate, adjusted according to individual sodium requirements. Hemodialysis fluid was routinely tested for bacterial growth (maximal level,  $< 200$  colony-forming units per milliliter). Vascular access was obtained with a dual-lumen hemodialysis catheter or with two catheters. Patients who required anticoagulant therapy received systemic unfractionated heparin. Only first-use, high-flux, synthetic dialyzer membranes (polysulfone [F60, Fresenius] or acrylonitrile [AN69, Hospal, Lyons, France]) were used.

### Dose of Hemodialysis

The patient's body weight and blood urea nitrogen level, the prescribed duration of hemodialysis, and the prescribed blood-flow rate were documented before each session. The actual duration of hemodialysis, the time-averaged blood-flow rate, and the total ultrafiltration volume were recorded at the end of each session. Post-treatment blood urea nitrogen levels were measured by the slow-flow method (with the blood-pump speed reduced to 50 ml per minute). Blood samples were obtained from the afferent sampling port before the blood reached the dialyzer.

The adequacy of hemodialysis was determined with the use of modeling of urea kinetics, based on the formula  $K \cdot t / V$ , where  $K$  denotes the rate of urea clearance by the dialyzer in milliliters per minute,  $t$  the duration of the treatment session in minutes, and  $V$  the volume of distribution of urea within the patient in liters. The minimal prescribed  $K \cdot t / V$  value was 1.2. (A value of 1.2 or higher is widely considered to indicate adequate hemodialysis in patients with end-stage renal disease.) The specific value was determined on the basis of the in vivo urea clearance for the dialyzer used, the prescribed duration of hemodialysis, and the pre-treatment body weight, which was multiplied by 0.60 for men and by 0.55 for women. The delivered dose of hemodialysis was determined on the basis of the single-pool  $K \cdot t / V$  value, corrected for ultrafiltration but not for the reappearance of urea nitrogen.<sup>8</sup>

Patients were treated and monitored according to accepted practices for intensive care. Parenteral nutrition was initiated if the oral intake of nutrients was deemed to be insufficient. For a patient who weighed 70 kg, the daily calorie intake was 27 kcal per kilogram of body weight (1.4 g of amino acids per kilogram, 3.4 g of glucose per kilogram, and 700 mg of lipids per kilogram) in a total volume of 1250 ml.

### Severity of Illness and Other Variables

The severity of illness was determined according to the score on the Acute Physiology, Age, and Chronic Health Evaluation (APACHE III) on the day of the first hemodialysis session.<sup>9</sup> Other variables included the cause of acute renal failure (determined on the basis of a chart review), the presence or absence of sepsis and of oliguria (defined as a urinary output of less than 400 ml in the previous 24 hours) at the initiation of hemodialysis, the reason for hemodialysis (uremia, fluid overload, or both), the number and duration of hemodialysis sessions, and the presence or absence of hypotensive episodes during hemodialysis (defined by a mean arterial blood pressure of less than 80 mm Hg or the need for intervention).

### Outcome Measurements

The primary end point of the study was survival 14 days after the last session of hemodialysis. We prospectively decided to analyze overall mortality rather than death from specific causes, because in patients with multiorgan failure, the cause of death may be uncertain. Secondary end points were the frequency of treatment-related complications and the duration of acute renal failure.

### Statistical Analysis

We calculated that with at least 80 patients for whom adequate data were available in each treatment group, the study would have a statistical power of 80 percent to detect an absolute difference in mortality of 20 percent between the groups, with a hypothetical mortality rate of 25 percent in the group that received treatment with daily hemodialysis and 45 percent in the group that received conventional alternate-day treatment. An independent data-monitoring committee reviewed protocol-related issues and safety on an ongoing basis and conducted an interim analysis after 72 patients had been enrolled. The final analysis was performed after 160 patients had been enrolled.

Multiple regression analysis was used to determine the effect of such variables as age, sex, the cause of acute tubular necrosis, the presence or absence of oliguria, the APACHE III score, and the assigned treatment on the risk of death during acute renal failure. All statistical tests (unpaired t-tests for continuous variables and Fisher's exact test for discrete variables) were two-sided. P values that were less than 0.05 were considered to indicate statistical significance. Statistical analyses were performed with SAS software (SAS Institute, Cary, N.C.).

## RESULTS

### Patients

The study was conducted from January 1993 through September 1998. A total of 172 patients with acute renal failure who required hemodialysis were eligible for enrollment. Eleven patients declined participation, and one patient was subsequently found not to be eligible because of prior hemodialysis, which had been performed to eliminate contrast medium. These 12 patients were excluded from the study.

A total of 160 patients were assigned in alternating order to the two treatment regimens. Fourteen patients were withdrawn during the course of the study, before the final data analysis: two had biopsy-proven, rapidly progressive glomerulonephritis (Goodpasture's disease), six were switched to continuous renal-replacement therapy because of clinical deterioration, and six required surgery during the first week of the study.

Of the remaining 146 patients, 72 patients received hemodialysis every other day, and 74 received daily treatment (Fig. 1). The base-line characteristics of the two treatment groups were similar (Table 1).

### Hemodialysis

The mean duration of the hemodialysis sessions, the average blood-flow rate, and the mean prescribed and delivered doses did not differ significantly between the two groups. However, the delivered dose was significantly lower than the prescribed dose in

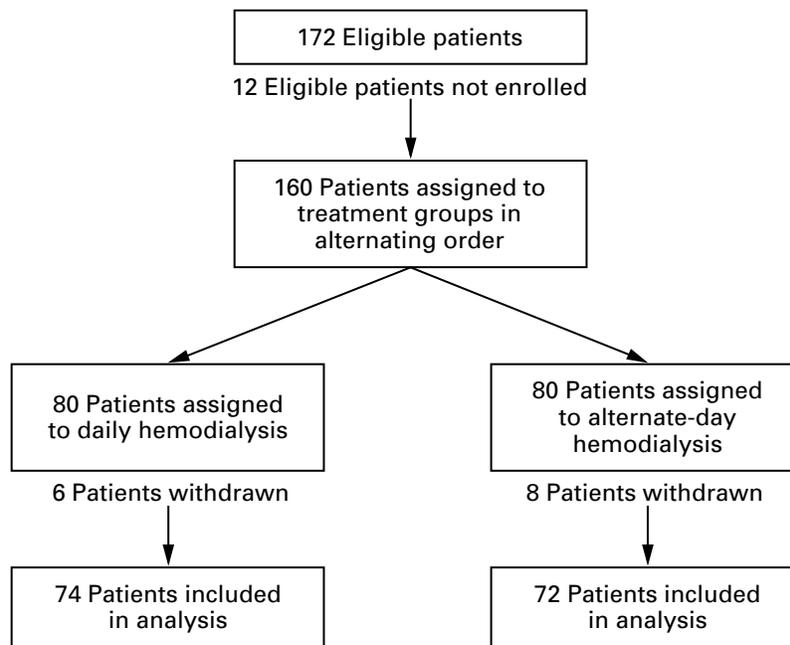
each group ( $P < 0.001$ ) (Table 2). The pretreatment small-solute levels and the proportion of patients with volume overload before the initiation of dialysis did not differ significantly between the treatment groups.

Daily hemodialysis resulted in better control of uremia than did alternate-day hemodialysis. The mean ( $\pm$ SD) values for time-averaged blood urea nitrogen and serum creatinine levels were  $60 \pm 20$  mg per deciliter ( $21.4 \pm 7.1$  mmol per liter) and  $5.3 \pm 1.2$  mg per deciliter ( $468.5 \pm 106.1$   $\mu$ mol per liter), respectively, in the daily-hemodialysis group and  $104 \pm 18$  mg per deciliter ( $37.1 \pm 6.4$  mmol per liter) and  $9.5 \pm 1.2$  mg per deciliter ( $839.8 \pm 106.1$   $\mu$ mol per liter), respectively, in the conventional-hemodialysis group ( $P < 0.001$  for both comparisons between the groups). The mean ultrafiltration volume during each session was  $1.214 \pm 0.464$  liters in the daily-hemodialysis group and  $3.486 \pm 0.262$  liters in the conventional-hemodialysis group ( $P < 0.001$ ). The mean percentage of sessions during which hypotensive episodes occurred was  $5 \pm 2$  percent for daily hemodialysis and  $25 \pm 5$  percent for conventional hemodialysis ( $P < 0.001$ ). Among the patients who initially had normal urinary output, oliguria developed in 30 of the 41 patients (73 percent) in the conventional-treatment group and in 8 of the 38 patients (21 percent) in the daily-hemodialysis group. More patients in the conventional-hemodialysis group than in the daily-hemodialysis group had the systemic inflammatory response syndrome or sepsis (33 vs. 16 [46 percent vs. 22 percent],  $P = 0.005$ ), respiratory failure (50 vs. 26 [69 percent vs. 35 percent],  $P < 0.001$ ), changes in mental status (50 vs. 28 [69 percent vs. 38 percent],  $P = 0.008$ ), or gastrointestinal bleeding (26 vs. 11 [36 percent vs. 15 percent],  $P = 0.007$ ), although the two groups had similar rates of coexisting conditions at enrollment.

### Outcomes

The overall mortality among all patients enrolled was 37 percent (59 of the 160 patients died). The overall mortality, according to the intention-to-treat approach, differed significantly between the two treatment groups: 22 of the 80 patients (28 percent) in the daily-hemodialysis group died, as compared with 37 of the 80 (46 percent) in the conventional-hemodialysis group ( $P = 0.01$ ) (Table 3).

Among the patients who completed the trial (i.e., in the efficacy analysis), 19 patients (26 percent) in the daily-hemodialysis group and 31 in the conventional-hemodialysis group (43 percent) died ( $P = 0.04$ ). The overall mortality was 34 percent. The two noneligible patients with Goodpasture's disease, both of whom were assigned to daily hemodialysis, survived. All six patients with clinical deterioration who were switched to continuous renal-replacement ther-



**Figure 1.** Patients Enrolled in the Study, Assigned to Daily or Alternate-Day Hemodialysis, and Included in the Analysis. Of the 12 eligible patients who were not enrolled, 11 declined to participate, and 1 was subsequently found to be ineligible. Among the six patients in the daily-hemodialysis group who were withdrawn from the study, the reasons for withdrawal were the development of glomerulonephritis (Goodpasture's disease) in two patients, a switch to continuous renal-replacement therapy because of clinical deterioration in two, and the need for surgery in two. Among the eight patients assigned to alternate-day hemodialysis who were withdrawn, four were withdrawn because of a switch to continuous renal-replacement therapy, and four because of the need for surgery.

apy died (two of the patients had been assigned to the daily regimen and four to the alternate-day regimen). Three of the six patients who required surgery died (one who had been assigned to the daily regimen and two who had been assigned to the alternate-day regimen).

Daily hemodialysis was associated with a significantly shorter time to the recovery of renal function (calculated as the duration of treatment with hemodialysis) than was conventional hemodialysis ( $9 \pm 2$  days vs.  $16 \pm 6$  days,  $P=0.001$ ) (Table 3). The analysis of recovery of renal function included both survivors and nonsurvivors, because a few nonsurvivors had a partial recovery of renal function before they died. All the surviving patients except the two with Goodpasture's disease had full recovery of renal function.

Multiple logistic-regression analysis demonstrated that four of the tested variables had a significant effect on survival. A greater severity of illness, as indicated by the APACHE III score, and the presence of sepsis at the time of enrollment were negatively cor-

related with survival. Normal urinary output at the time of enrollment and assignment to the regimen of daily hemodialysis were positively correlated with survival (Table 4).

## DISCUSSION

Our prospective study shows that the relation among acute renal failure, coexisting conditions, and death in critically ill patients is more complicated than is generally recognized. Undoubtedly, the high mortality associated with acute renal failure is determined by the severity of the underlying illness or coexisting condition that confers a predisposition to acute renal failure. In our study, the clinically relevant difference in mortality between the patients who received daily hemodialysis and those who received hemodialysis on alternate days suggests that more frequent hemodialysis decreases the risk of fatal nonrenal complications of acute renal failure. In contrast to our findings, the mortality rates reported by Gillum et al.<sup>5</sup> did not differ significantly between the group that received intensive hemodialysis and the group

**TABLE 1.** CHARACTERISTICS OF THE PATIENTS AT ENROLLMENT.\*

CHARACTERISTIC	ALTERNATE-DAY HEMODIALYSIS (N=72)	DAILY HEMODIALYSIS (N=74)
Age — yr	61±14	59±13
Sex — no.		
Male	40	40
Female	32	34
Intensive care setting — no.		
Medical	44	42
Surgical	28	32
Cause of acute renal failure — no. (%)		
Hypotension	42 (58)	37 (50)
Sepsis	23 (32)	30 (41)
Nephrotoxins	7 (10)	7 (9)
Blood urea nitrogen — mg/dl	91±13	88±16
Serum creatinine — mg/dl	4.9±1.4	4.6±1.0
Oliguria — no. (%)	31 (43)	36 (49)
APACHE III score†	85±9	89±7

\*Plus-minus values are means ±SD. To convert the values for blood urea nitrogen to millimoles per liter, multiply by 0.357. To convert the values for creatinine to micromoles per liter, multiply by 88.4.

†APACHE denotes Acute Physiology, Age, and Chronic Health Evaluation. Scores can range from 0 to 299; higher scores indicate more severe illness.

that received nonintensive hemodialysis (59 percent and 47 percent, respectively). In this early study, however, the lack of modern hemodialysis techniques such as volumetric control of ultrafiltration, biocompatibility of the hemodialysis components, and individual adjustments of fluid and sodium requirements may have resulted in greater morbidity during treatment, thereby counteracting the effects of the improvement in the control of uremia.

The purpose of hemodialysis is both to provide a substitute for renal clearance of metabolic byproducts and to control volume, allowing the recovery of renal function while maintaining homeostasis. Our study suggests that daily hemodialysis offers a number of advantages over alternate-day hemodialysis and has many of the clinical benefits of continuous renal-replacement techniques.

Daily hemodialysis was well tolerated by our patients, permitting intensive nutritional support without hypotensive episodes. As a result, the rates of multiorgan failure, fluid imbalance, and other events that typically result in increased mortality were lower in the group of patients who received daily hemodialysis than in the group that received hemodialysis on alternate days. The underlying reason for the lower mortality in the daily-hemodialysis group remains speculative, because autopsy could not be performed in all the patients who died.

Higher doses of hemodialysis, although beneficial

**TABLE 2.** CHARACTERISTICS OF HEMODIALYSIS SESSIONS.\*

CHARACTERISTIC	ALTERNATE-DAY HEMODIALYSIS	DAILY HEMODIALYSIS
Duration of session (hr)	3.4±0.5	3.3±0.4
Blood-flow rate (ml/min)	243±25	248±45
Dose (K·t/V)†		
Prescribed	1.21±0.09	1.19±0.11
Delivered	0.94±0.11‡	0.92±0.16‡
Weekly delivered	3.0±0.6	5.8±0.4

\*Values are means ±SD.

†The dose is the value obtained with the formula  $K \cdot t / V$ , where K denotes the rate of urea clearance by the dialyzer in milliliters per minute, t the duration of the treatment session in minutes, and V the volume of the distribution of urea in liters. The weekly delivered dose was calculated on the basis of a mean of 3.2 sessions per week in the alternate-day hemodialysis group and 6.2 sessions per week in the daily-hemodialysis group.

‡P<0.001 for the comparison with the prescribed dose in the same group.

**TABLE 3.** OUTCOMES ACCORDING TO TREATMENT GROUP.\*

	ALTERNATE-DAY HEMODIALYSIS (N=80)	DAILY HEMODIALYSIS (N=80)	P VALUE
Mortality — no. (%)†	37 (46)	22 (28)	0.01
Resolution of acute renal failure — days	16±6	9±2	0.001

\*Plus-minus values are means ±SD.

†Mortality was calculated according to the intention to treat.

in critically ill patients, are ill defined by current methods of measuring the dose, which have been extrapolated from studies involving patients with end-stage renal disease (the two groups have differences in total body water, the protein catabolic rate, and vascular access). We found that a higher frequency of hemodialysis resulted in a higher value for the weekly delivered  $K \cdot t / V$  dose. This finding calls into question the concept of equivalent urea-kinetics modeling in acute and chronic renal failure.<sup>10</sup> Nevertheless, all studies of urea-kinetics modeling in patients with acute renal failure have shown that the delivered dose did not match the prescribed dose.<sup>11-13</sup> In fact, the actual values for in vivo clearance of urea in our patients were almost 25 percent lower than the

**TABLE 4.** ODDS RATIOS FOR DEATH ACCORDING TO SELECTED VARIABLES, FROM THE MULTIPLE LOGISTIC-REGRESSION ANALYSIS.

VARIABLE	ODDS RATIO FOR DEATH (95% CI)*	P VALUE
Alternate-day hemodialysis (vs. daily hemodialysis)	3.92 (1.68–9.18)	0.002
APACHE III score†	1.06 (1.01–1.12)	0.02
Oliguria (vs. normal urinary output)‡	3.02 (1.35–6.77)	0.007
Sepsis (vs. no sepsis)	3.27 (1.43–7.50)	0.005

\*Each odds ratio was adjusted for the other variables listed.

†Scores can range from 0 to 299 (physiology, 0 to 252; chronic health evaluation, 0 to 23; age, 0 to 24). A higher score on the Acute Physiology, Age, and Chronic Health Evaluation (APACHE III) indicates more severe illness. Patients with higher scores had a higher mortality rate.

‡Oliguria was defined as a urinary output of less than 400 ml per day.

calculated values and might have been even lower if double-pool kinetic  $K \cdot t/V$  values had been used.<sup>14</sup> Furthermore, previous studies have shown that in most patients with acute renal failure, the delivered  $K \cdot t/V$  value was less than 1.2, which is considered the minimal adequate dose in patients with stable end-stage renal disease.

We suggest that daily hemodialysis be prescribed for the treatment of hypercatabolic or oliguric or anuric acute renal failure, in accordance with theoretical prescription models for the use of hemodialysis in patients with acute renal failure. Clark et al.<sup>15</sup> predicted a required treatment frequency of 4.4 hemodialysis sessions per week for a 70-kg patient in order to achieve a mean blood urea nitrogen level of 80 mg per deciliter (28.6 mmol per liter) and 6.0 sessions per week to achieve a blood urea nitrogen level of 60 mg per deciliter (21.4 mmol per liter). In our study, the mean post-hemodialysis weight was 72 kg, and the mean number of hemodialysis sessions was 6.2 per week in the daily-hemodialysis group.

Despite fundamental differences between acute renal failure and end-stage renal disease, patients with acute renal failure are given doses of hemodialysis that would be considered inadequate even for patients

with stable end-stage renal disease. Strict control of azotemia and fluid volume by means of daily hemodialysis in patients with acute renal failure may improve survival, at least among patients with an intermediate risk of death, as in our study. Therefore, we believe that alternate-day hemodialysis should no longer be considered adequate for critically ill patients with acute renal failure.

*We are indebted to the patients who participated in this study and to the many members of the staff at our hospital who contributed to the care of the patients.*

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