Diuretics, Mortality, and Nonrecovery of Renal Function in Acute Renal Failure

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ACUTE RENAL FAILURE (ARF) IN hospitalized patients may be associated with low, normal, or excess extracellular volume, depending on the cause of the ARF, accompanying conditions (eg, heart failure, liver disease), and patterns of administration of crystalloids and colloids. Diuretic agents are frequently given to augment renal salt and water excretion in the setting of extracellular volume overload.

Diuretics are also frequently given during ARF in an effort to "convert" oliguric to nonoliguric ARF, since oliguria has been recognized as a proxy for the severity of ARF and the likelihood of requiring dialysis.[1-4] Despite the ubiquity of this practice, there is scant evidence that diuretics provide any material benefit to patients with ARF. Indeed, the "conversion" of oliguric to nonoliguric ARF may reflect the severity of disease (diuretic-responsive ARF) rather than a valid (and favorable) response to therapy.[5-7] Moreover, the use of diuretics may increase the risk of ARF when given before radiocontrast exposure[8-10] and in other clinical settings,[11-13] raising the possibility that diuretics may be harmful in patients with established ARF. Several randomized clinical trials have explored the use of diuretics in established ARF and have not shown benefit in survival or recovery of renal function, although all studies were hampered by low statistical power.[14-17]

We hypothesized that the use of diuretics during ARF would be associated with an increase in mortality, hospital length of stay, and nonrecovery of renal function in critically ill patients with ARF due to either direct effects or indirect effects of delaying dialytic sup-

Context Acute renal failure is associated with high mortality and morbidity. Diuretic agents continue to be used in this setting despite a lack of evidence supporting their benefit.

Objective To determine whether the use of diuretics is associated with adverse or favorable outcomes in critically ill patients with acute renal failure.

Design Cohort study conducted from October 1989 to September 1995.

Patients and Setting A total of 552 patients with acute renal failure in intensive care units at 4 academic medical centers affiliated with the University of California. Patients were categorized by the use of diuretics on the day of nephrology consultation and, in companion analyses, by diuretic use at any time during the first week following consultation.

Main Outcome Measures All-cause hospital mortality, nonrecovery of renal function, and the combined outcome of death or nonrecovery.

Results Diuretics were used in 326 patients (59%) at the time of nephrology consultation. Patients treated with diuretics on or before the day of consultation were older and more likely to have a history of congestive heart failure, nephrotoxic (rather than ischemic or multifactorial) origin of acute renal failure, acute respiratory failure, and lower serum urea nitrogen concentrations. With adjustment for relevant covariates and propensity scores, diuretic use was associated with a significant increase in the risk of death or nonrecovery of renal function (odds ratio, 1.77; 95% confidence interval, 1.14-2.76). The risk was magnified (odds ratio, 3.12; 95% confidence interval, 1.73-5.62) when patients who died within the first week following consultation were excluded. The increased risk was borne largely by patients who were relatively unresponsive to diuretics.

Conclusions The use of diuretics in critically ill patients with acute renal failure was associated with an increased risk of death and nonrecovery of renal function. Although observational data prohibit causal inference, it is unlikely that diuretics afford any material benefit in this clinical setting. In the absence of compelling contradictory data from a randomized, blinded clinical trial, the widespread use of diuretics in critically ill patients with acute renal failure should be discouraged.

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port. To explore these questions, we examined data from a cohort of critically ill patients with ARF. Recognizing the limitations of comparing therapies that have not been randomly assigned, we attempted to adjust for confounding and practice variation with regression methods complemented by propensity scores.

METHODS
Study Cohort

Data were collected on all intensive care unit (ICU) patients with ARF who received nephrology consultation at 4 teaching hospitals (University of California San Diego Medical Center, San Diego Veterans Affairs Medical Center, San Diego Naval Hospital, and University of California, Irvine, Medical Center) from October 1989 to September 1995. Acute renal failure was defined using standard laboratory parameters. For patients with no history of kidney disease or known laboratory values, ARF was defined either by a blood urea nitrogen (BUN) level of 40 mg/dL or higher ($\geq$14.3 mmol/L) or a serum creatinine level of 2.0 mg/dL or higher ($\geq$177 µmol/L). For others, ARF was defined by a sustained rise in serum creatinine levels of 1 mg/dL or more ($\geq$88.4 µmol/L) compared with baseline. Exclusion criteria included previous dialysis, kidney transplantation, urinary tract obstruction, and hypovolemia. Informed consent was obtained from all study participants or their next-of-kin.

Patients were followed up prospectively from the time of initial nephrology service consultation through hospital discharge. A total of 851 ARF cases were initially evaluated. No information on vital status was available in 31 patients (4%). Of the 820 remaining, data sufficient to calculate generic and disease-specific severity of illness scores for risk adjustment were available in 605 patients (74%). Information on the use of diuretics from the initial ICU consultation day onward was available in 552 patients (91%), who comprised the analytic sample.

The primary outcome measure was all-cause hospital mortality. We also considered the combined end point of either mortality or nonrecovery of renal function and lengths of ICU and hospital stay. Recovery of renal function was defined as being dialysis independent with a serum creatinine level of 2.0 mg/dL or less ($\leq$177 µmol/L) or no more than 20% higher than baseline at the time of hospital discharge. The origin of ARF was classified as follows: ischemic acute tubular necrosis, nephrotoxic acute tubular necrosis, multisystem disorder, or uncertain.

Baseline vital signs, hemodynamic data (where available), and laboratory data were recorded for the first ICU day and each day from the time of nephrology consultation. Renal function was assessed daily from records of urine output, BUN level, and serum creatinine level. Generic and disease-specific severity-of-illness scores were computed on each successive ICU day. We determined the number of organ systems in failure based on a modification of the criteria of Chang et al.[18] We used published criteria for each organ system failure.[19] We categorized patients as taking or not taking diuretics on each of the first 7 days following consultation and "ever" or "never" using diuretics during this week. Additionally, we categorized patients treated with 1 vs 2 or more diuretic agents and identified specific medications and daily doses for secondary analyses. Oliguria was defined as urine output of less than 400 mL/d. To estimate the response to diuretics, we calculated the total daily dose of loop diuretic (in furosemide equivalents) divided by the total urine output in milliliters. For this calculation, 1 mg of bumetanide was considered to be equivalent to 40 mg of furosemide.

Statistical Analysis

Continuous variables were expressed as mean (SD) (or 10% and 90% confidence limits) or median and compared with the t test or the Wilcoxon rank sum test where appropriate. Categorical variables were expressed as proportions and compared with the Mantel-Haenszel χ^2 test. Variables with significant associations on univariate screening were considered candidates for multivariable analysis, along with age, sex, and race. Multivariable logistic regression was performed using backward variable selection, with variable exit criteria set at $P<.05$. Variables not selected by the automated procedure were added back into models individually to evaluate for residual confounding. The area under the receiver operating characteristic curve was used to assess model discrimination.[20] Calibration was estimated using the Hosmer-Lemeshow goodness-of-fit test.[21]

In addition to adjusting for significant covariates in multivariable regression, residual confounding and selection effects were addressed using propensity scores.[22] To develop the propensity score, we included in a separate multivariable logistic regression analysis all factors that differed among the diuretic and no diuretic groups, using a more liberal significance criterion of $P<.25$. With diuretic use as the dependent variable, we fit a model predicting the likelihood or "propensity" of diuretic use. We then incorporated the propensity score as a covariate in a logistic regression model using mortality as the dependent variable. Inclusion of the propensity score as a covariate in a multivariable regression theoretically normalizes the likelihood of treatment (in this case, diuretics) and may effectively adjust for unobserved confounding and selection bias, thereby refining regression estimates. We performed these analyses again using the combined end point of mortality or nonrecovery of renal function. Although the primary analysis incorporated data from the day of consultation, we conducted companion analyses for other time points. Finally, we used the Kaplan-Meier product limit method[23] to calculate the time to death or the provision of dialysis for ARF (censored at day 60) and compared survival curves with the logrank test. $P\leq.05$ (2-tailed) was considered statistically significant. All analyses were conducted using SAS statistical software, version 8 (SAS Institute Inc, Cary, NC).

RESULTS
Factors Associated With Diuretic Use

Characteristics for the diuretic and no diuretic groups on the day of nephrology consultation are shown in TABLE 1. Few data were missing, except for the invasive physiologic variables, which were individually available in 40% to 76% of patients. The mean age was significantly higher and BUN and creatinine levels significantly lower among diuretic-treated patients on day 1 of ICU consultation. There were no significant differences in APACHE II (Acute Physiology and Chronic Health Evaluation II) or APACHE III scores. Among patients who underwent invasive hemodynamic monitoring, those with higher pulmonary capillary wedge pressure and lower cardiac index were more likely to be given diuretics. The proportion of patients given diuretics overall declined from 59% to 44% to 40% during the first 3 days following consultation, although an increasing fraction of those taking diuretics were nonoliguric (59% to 80% to 86%). Although there were initially no differences in severity-of-illness scores, mean APACHE III scores were lower in diuretic-treated patients on day 2 (91.9 vs 87.3, $P = .08$) and day 3 (92.8 vs 82.7, $P < .001$). Sixty-six (29%) of the 226 patients not taking diuretics at the time of consultation were given diuretics during the following week.

Calculation of the Propensity Scores

The following equations were used to derive the propensity score for diuretic use on the first day of consultation:

(1)
$X = (\text{Age} \times 0.113) - (\text{Nephrotoxic Etiology of ARF} \times 0.5645) - (\text{BUN} \times 0.00727) + (\text{Acute Respiratory Failure} \times 0.5837) + (\text{History of Congestive Heart Failure} \times 0.8803) - 0.4394$

(2)
$\text{Propensity Score} = (e \text{ or } 2.7182818^X)/[1 + (e \text{ or } 2.7182818^X)]$

The propensity score itself can be interpreted as the likelihood of being given diuretics based on the observed array of covariates included in the model. The mean propensity score was 0.59 (ie, the fraction of patients given diuretics on day 1); the range was 0.225×10^{-6} to 0.910.

Table 1. Baseline Patient Characteristics on First Day of Nephrology Consultation*

Demographics and History	No Diuretic (n = 226)	Diuretic (n = 326)	P Value
Age, mean (SD), y	53.8 (18.0)	58.1 (17.1)	.005†
Male, No. (%)	168 (74)	230 (71)	.33
Race, No. (%)			
White	125 (55)	203 (62)	
African American	50 (22)	46 (14)	
Hispanic	2 (1)	5 (2)	.12†
Asian	21 (9)	37 (11)	
Other or unknown	28 (12)	35 (11)	
Surgical, No. (%)	77 (65)	96 (62)	.28
Oliguria, No. (%)	71 (32)	100 (31)	.75
ARF on CRI, No. (%)	56 (25)	83 (26)	.86
Hyperkalemia, No. (%)‡	17 (8)	29 (9)	.57
History of CHF, No. (%)	30 (13)	87 (27)	<.001†
History of liver disease, No. (%)	49 (22)	54 (17)	.13†
Etiology of acute renal failure, No. (%)			
Ischemic	98 (43)	128 (40)	.34
Nephrotoxic	28 (12)	61 (19)	.05†
Multifactorial	43 (19)	49 (15)	.22†
Unknown	57 (25)	88 (27)	.64
Renal function			
Mean (SD) BUN, mg/dL	72.3 (43.4)	61.6 (34.6)	.001†
Mean (SD) creatinine, mg/dL	4.1 (3.3)	3.6 (1.9)	.02†
Median urine output, mL/d	955	888	.49
Physiologic indicators			
Temperature, mean (SD), °C	37 (1.2)	37 (1.1)	.63
Heart rate, mean (SD), beats/min	102 (24)	100 (22)	.24†
Systolic blood pressure, mean (SD), mm Hg	122 (33)	117 (29)	.07†
Diastolic blood pressure, mean (SD), mm Hg	61 (17)	59 (17)	.30
Arterial pressure, mean (SD), mm Hg	81 (21)	78 (20)	.19†
Central venous pressure, mean (SD), mm Hg§	15 (7)	15 (6)	.77
Pulmonary artery wedge pressure, mean (SD), mm Hg§	18 (8)	20 (7)	.04
Cardiac output, mean (SD), L/min§	8.5 (3.9)	6.9 (3.1)	<.001
Cardiac index, mean (SD), L/min/m²§	4.6 (2.0)	3.7 (1.6)	<.001
Systemic vascular resistance, mean (SD), dynes·s·cm⁻⁵§	728 (429)	903 (811)	.02
P_{O_2}, mean (SD), mm Hg§	102 (48)	98 (49)	.43
P_{CO_2}, mean (SD), mm Hg§	35 (9)	37 (9)	.11
pH, mean (SD)§	7.3 (0.1)	7.4 (0.1)	.21
APACHE III score, mean (SD)§	86.7 (32.9)	86.1 (30.5)	.84
APACHE II score, mean (SD)§	19.0 (7.8)	18.8 (7.4)	.54
Organ system failure, No. (%)			
Respiratory	143 (64)	241 (74)	.01†
Cardiac	75 (33)	148 (45)	.005†
Liver	75 (33)	109 (33)	.98
Hematologic	73 (32)	92 (28)	.29
Central nervous system	82 (36)	112 (34)	.61

*ARF indicates acute renal failure; CRI, chronic renal insufficiency; CHF, congestive heart failure; BUN, blood urea nitrogen; and APACHE, Acute Physiology and Chronic Health Evaluation. To convert milligrams per deciliter to micromoles per liter (creatinine), multiply by 88.4. To convert milligrams per deciliter to millimoles per liter (BUN), multiply by 0.357.
†Entry included as candidate variable for propensity score; physiologic variables not included in propensity score because not available on all or nearly all patients.
‡Hyperkalemia was defined as a potassium level of more than 6 mEq/L.
§For selected physiologic indicators, sample sizes range from 90 to 180 for "no diuretic" group and 133 to 260 for "diuretic" group.

Table 2. Effect of Diuretics on Mortality and Nonrecovery of Renal Function Compared With No Diuretic Use*

Variable	OR (95% CI)		
	Unadjusted	Covariate Adjusted	Covariate and Propensity Score Adjusted
In-hospital mortality	1.37 (0.97-1.92)	1.65 (1.05-2.58)	1.68 (1.06-2.64)
Nonrecovery of renal function	1.53 (1.08-2.15)	1.70 (1.14-2.53)†	1.79 (1.19-2.68)§
Death or nonrecovery	1.48 (1.02-2.12)	1.74 (1.12-2.68)‡	1.77 (1.14-2.76)‖

*Covariate adjusted for age; sex; log urine output; serum creatinine level; blood urea nitrogen level; respiratory, hepatic, and hematologic failure; and heart rate. The referent group was no diuretics; time was first day of intensive care unit consultation. OR indicates odds ratio; CI, confidence interval.
†Area under receiver operating characteristic (ROC) curve = 0.76; goodness-of-fit χ^2 P = .89.
‡Area under ROC curve = 0.82; goodness-of-fit χ^2 P = .39.
§Area under ROC curve = 0.85; goodness-of-fit χ^2 P = .84.
‖Area under ROC curve = 0.81; goodness-of-fit χ^2 P = .58.

Mortality and Nonrecovery of Renal Function and Diuretic Use

Two hundred ninety-four (53%) of 552 patients died in-hospital. Fifty-six (19%) of 294 patients who died recovered renal function before death. Among the 258 patients who survived (47%), 17 (7%) were dialysis dependent after discharge. We therefore fit distinct logistic regression models for in-hospital mortality, nonrecovery of renal function, and the combined outcome of mortality or nonrecovery of renal function (**TABLE 2**). In the covariate-adjusted models, we included age, sex, and the first consultation day values for heart rate, BUN, creatinine, log urine output, and respiratory, hematologic, and liver failure based on previous analyses.[24] Diuretic use was associated with a 68% (95% confidence interval [CI], 6%-164%) increase in in-hospital mortality and a 77% (95% CI, 14%-176%) increase in the odds of death or nonrecovery of renal function. In these models, there were no significant interactions between diuretic use and urine output. Neither a history of congestive heart failure nor the presence of cardiac organ system failure explained the increased risks observed.

There was no difference in hospital length of stay by use of diuretics on the first day of consultation (median, 21.5 vs 22.5 days; P = .95). However, subsequent diuretic use was associated with significantly longer lengths of stay (median difference, 4-10 days; all comparisons were at least P<.01 for each of con-

sultation days 2-7). The median time from consultation to first dialysis was also significantly prolonged among patients given diuretics (median difference, 1-2 days; P<.01 for each of consultation days 1-7).

Since many patients crossover as users and nonusers of diuretics, we also compared results of patients classified as "ever" vs "never" users of diuretics, excluding individuals who died within the first week following consultation. In these analyses (n=416), the odds ratio (OR) of death or nonrecovery of renal function in "ever" users of diuretics was 2.01 (95% CI, 1.26-3.20). These results remained statistically significant after covariate (OR, 3.15; 95% CI, 1.74-5.70) and covariate and day 1 propensity score adjustment (OR, 3.12; 95% CI, 1.73-5.62). As with the primary analyses, these models exhibited good discrimination and were well calibrated.

Single vs Combination Diuretic Use, Specific Diuretic Use, and Dosage

Several diuretic agents and diuretic combinations were used. Of the 326 patients given diuretics on ICU consultation day 1, 203 (62%) were given furosemide, 189 (58%) were given bumetanide, 106 (33%) were given metolazone, and 13 (4%) were given hydrodiuril. Loop and thiazide diuretics in combination were given to 105 patients (32%). The median (with 10%-90% range) doses of furosemide, bumetanide, and metolazone were 80 (20-
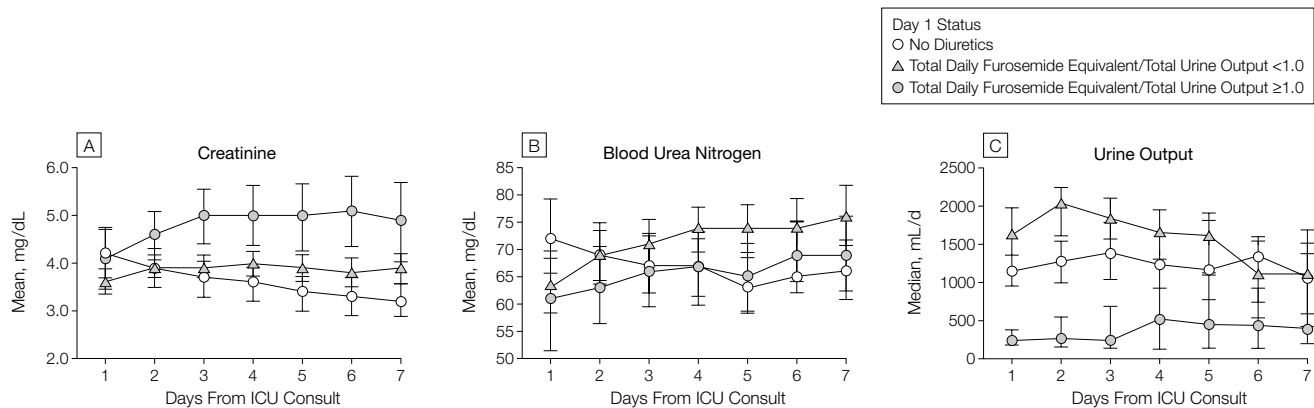
320), 10 (2-29), and 10 (5-20) mg/d, respectively. Although diuretic use was associated with mortality, nonrecovery of renal function, and prolonged time to initiation of dialysis, there were no significant differences among patients taking single vs combination diuretics for any of these parameters.

Index of Diuretic Responsiveness

Since higher doses of diuretics are often used in patients who are oliguric or have declining urine output, we calculated the furosemide dose equivalent per milliliter per day of urine output as an index of the degree of diuretic responsiveness and, potentially, the severity of renal injury. The median dose equivalent per milliliter ratio was 0.34 mg/mL (10%-90% range, 0.02-4.22). Expressed in clinical terms, the 10% to 90% ratio ranged from very responsive (1000 mL associated with a single 20-mg dose of furosemide) to very unresponsive (114 mL associated with 240 mg of furosemide given twice daily). We a priori selected a ratio of 1.0 to stratify analyses by diuretic responsiveness. Patients with a dose equivalent per milliliter ratio of 1.0 or higher on the day of consultation had a higher odds of death or nonrecovery compared with nonusers of diuretics (OR, 2.94; 95% CI, 1.61-5.36). In contrast, patients with a dose equivalent per milliliter ratio of less than 1.0 experienced no significant increase in risk (OR, 1.15; 95% CI, 0.79-1.68). Results were similar when analyses were stratified by a dose equivalent per milliliter ratio of 0.5 (OR, 2.75; 95% CI, 1.66-4.54; and OR, 0.97; 95% CI, 0.65-1.45; for dose equivalent per milliliter ratios of ≥0.5 and <0.5, respectively). In other words, the increase in risk was borne largely by patients who were relatively unresponsive to diuretics. Moreover, the risk associated with a high dose equivalent per milliliter ratio was magnified over time (day 2 following consultation: OR, 3.61; 95% CI, 1.58-8.21; day 3 following consultation: OR, 7.12; 95% CI, 1.67-30.27).

FIGURE 1 shows the relative differences in mean creatinine levels, mean

Figure 1. Time Trends in Mean Serum Creatinine Levels, Mean Blood Urea Nitrogen Levels, and Median Urine Output Among the 416 Patients Who Survived for at Least 7 Days After Nephrology Consultation in the Intensive Care Unit (ICU)

Day 1 Status
○ No Diuretics
△ Total Daily Furosemide Equivalent/Total Urine Output <1.0
◎ Total Daily Furosemide Equivalent/Total Urine Output ≥1.0

Groups are stratified by day 1 status: no diuretics vs diuretic therapy with response. To convert milligrams per deciliter to micromoles per liter, multiply by 88.4. To convert milligrams per deciliter to millimoles per liter, multiply by 0.357.

BUN levels, and median urine output for patients stratified by diuretic use and the dose equivalent per milliliter ratio, with values censored at the initiation of dialysis. **FIGURE 2** shows the association between the dose equivalent per milliliter ratio and the time to death or dialysis for ARF during hospitalization, comparing patients not taking diuretics and those with high and low dose equivalent per milliliter ratios (logrank χ^2, $P < .001$).

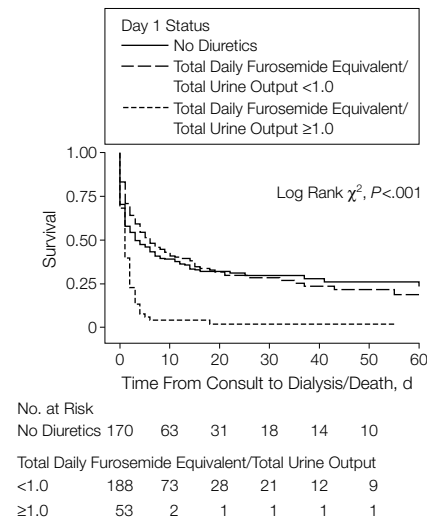## COMMENT

Diuretics have been widely used in ARF despite little evidence of benefit.[25,26] Indeed, several prospective clinical trials have evaluated the effect of loop diuretic agents, usually at high doses, in prevention and/or treatment of ARF.[14,17,27] Most studies[15-17] were relatively small and confounded by cointerventions such as low-dose dopamine hydrochloride or mannitol. Aside from augmenting urine output, few studies have demonstrated any material benefit of diuretics in ARF, whereas other studies have suggested potential deleterious effects.[12,26-28] For example, Lassnigg et al[12] showed that postoperative ARF (defined as an increase in serum creatinine level of ≥0.5 mg/dL [44 μmol/L]) was more frequent in patients given furosemide (15%) compared with dopamine (2%) or isotonic sodium chloride (0%).

In this study, 59% of patients were taking diuretics at the time of nephrology consultation and 12% started taking diuretics after consultation. Diuretic use at the time of consultation was significantly associated with older age, presumed nephrotoxic (rather than ischemic or multifactorial) ARF origin, a lower BUN level, acute respiratory failure, and a history of congestive heart failure. After adjusting for covariates associated with the risk of death,[24] diuretic use was significantly associated with in-hospital mortality and nonrecovery of renal function, even after adjustment for nonrandom treatment assignment using propensity scores.

Possible explanations for the associations observed include a direct toxic effect of diuretics or indirect effects either related or unrelated to renal function. Providers of care in ICUs may underestimate the severity of renal injury when urine output is sustained. Although we and others have shown oliguria to be associated with adverse outcomes in ARF,[19,24,29-33] it is unclear whether diuretic use modifies the effect of oliguria on mortality or nonrecovery of renal function. We have previously shown that oliguria and a low serum creatinine level (associated either with low creatinine generation or dilution with extracellular volume overload) are the 2

Figure 2. Time to Death or Dialysis From Day of Consultation in Intensive Care Unit

Day 1 Status
—— No Diuretics
– – – Total Daily Furosemide Equivalent/Total Urine Output <1.0
······ Total Daily Furosemide Equivalent/Total Urine Output ≥1.0

Log Rank χ^2, $P < .001$

No. at Risk

No Diuretics 170 63 31 18 14 10

Total Daily Furosemide Equivalent/Total Urine Output

<1.0 188 73 28 21 12 9

≥1.0 53 2 1 1 1 1

Groups are stratified by day 1 status. For those patients who were diuretic resistant (furosemide equivalent per milliliter ratio ≥1.0), the No. at risk for days 1, 2, 3, and 5 were 35, 19, 10, and 3, respectively. Analysis includes 411 of the 416 patients who survived at least 7 days after nephrology consultation in the intensive care unit. Data are excluded for 5 patients who died at an unknown time.

factors most closely related to delay in nephrology consultation among patients who have ARF on ICU admission.[34] If nonoliguria delays recognition of ARF or recognition of the severity of ARF, then the use of diuretics might influence ICU management, including

the timing of dialysis. The relative 1- to 2-day delay in time from consultation to initiation of dialysis in patients taking diuretics suggests that practice patterns differ among patients taking and not taking diuretics. If persons die from rather than with ARF, as others and we have suggested,[35-37] delay in initiation of dialysis (waiting for a response to diuretics) may have untoward effects. These effects could include the worsening of respiratory, cardiovascular, central nervous system, and immune function due to volume overload and the effects of uremia.

In addition to the major findings linking diuretic use to mortality and nonrecovery, we highlighted the potential importance of severity of renal injury in determining ARF outcomes. Biopsies are rarely performed in patients with ARF, and no reliable, valid index of ARF severity has yet been developed. In this study, we showed that the increased risk associated with diuretic use was largely borne by those individuals who were relatively resistant to the agents, confirming and extending the findings previously reported by Cantarovich and Verho[38] in a multicenter French study. In addition, we found that the degree of diuretic resistance on consultation day 1 predicted subsequent changes in BUN and creatinine concentrations, with the former paradoxically rising faster in more diuretic-responsive patients. If this index (total daily furosemide dose equivalent per milliliter per day of urine output) were validated in other settings, it might serve as a means to risk stratify patients early in ARF. In other words, if a patient with early ARF has low or declining urine output despite high doses of loop diuretics, then further delay in instituting corrective therapy may not be warranted, since the likelihood of death or the need for dialysis in the short term is extremely high. In this way, the practice of a "diuretic challenge" need not be abandoned but rather modified. Ultimately, identifying the optimal timing of initiation of dialysis (or hemodiafiltration) in ARF will have to be determined in a prospective randomized trial.

There are several important limitations to this study. Even with propensity score adjustment, we cannot truly evaluate the *effect* of diuretics, as we could in a prospective randomized trial. Although the propensity score can adjust for confounding by indication and selection bias, we cannot eliminate residual confounding due to unobserved factors. We had no kidney biopsy data and no method by which direct toxic injury induced by diuretics could be proved or refuted. Therefore, we were unable to derive any mechanistic explanation for the findings described herein. Although this was a multicenter study, the hospitals were all within a single region, and the results described may not be generalizable to other regions or practice settings (eg, settings where the availability of dialysis services may differ). These patients were critically ill. Therefore, we cannot extrapolate the results to individuals with less severe forms of ARF or with ARF in the absence of critical nonrenal disease. Moreover, since all patients included in this study had a significant increase in serum creatinine levels, we cannot infer that diuretics would be harmful in patients very early in ARF, although there is no evidence that they would be of benefit based on studies in ARF prevention.[27]

Although the data were collected mainly in the 1990s, ARF practice patterns have not changed significantly since that time. In randomized clinical trials (1995-1999) that tested the efficacy of other agents known to augment urine output (eg, atrial natriuretic peptide, low-dose dopamine), 43% to 55% of patients with ARF in the ICU were treated with diuretics, even with sustained oliguria.[28,39] In a recent survey of the European Workgroup of Cardiothoracic Intensivists,[12] 11 of 38 used continuous infusions of furosemide for "renoprotection" and 34 of 38 used furosemide bolus injections when urine output decreased to less than 0.5 mL/kg per hour. Although some nonrenal ICU therapies (eg, methods of mechanical ventilation, frequency of pulmonary artery catheter use, choice of antibiot-

ics) have changed during the past several years, it is unlikely that these changes have modified the relations among diuretic use and outcomes in critically ill patients with ARF.

In summary, we determined that diuretic use was associated with adverse outcomes in ARF. The increase in mortality and nonrecovery of renal function observed may be due to a direct deleterious effect of diuretic agents, a delay in the institution of renal support (in effect, forestalling dialysis with volume overload or with anticipated reversal of azotemia), or other or unknown factors. Although we cannot securely determine that diuretics are harmful, it is highly unlikely that diuretics afford ARF patients any material benefit. In the absence of compelling contradictory data from a randomized, blinded clinical trial, we should discourage the widespread use of high-dose diuretics in critically ill patients with ARF.

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It is possible to fly without motors, but not without knowledge and skill.
　　—Wilbur Wright (1867-1912)