A Multicenter Comparison of Dialysis Membranes in the Treatment of Acute Renal Failure Requiring Dialysis

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Abstract. The mortality of patients with acute renal failure (ARF) remains high, and in several large studies approaches 60%. This mortality is particularly high in patients with ARF who require dialysis and has not changed substantially over several years, despite the introduction of major advances in monitoring and treatment. Increasing prevalence of comorbidities has been suggested as the major factor in this persistently high mortality. This study investigates the potential role of the dialysis membrane on patient outcome in a prospective multicenter study of 153 patients with ARF requiring dialysis. The membrane assignment was made in alternating order and was limited to membranes with low complement activation (Biocompatible [BCM]) and cellulosic, high complement activation (Bioincompatible [BICM]). Both types of membranes were low-flux membranes. Patients were dialyzed with the assigned membrane until recovery, discharge from hospital, or death. The severity of illness of each patient was assessed using the APACHE II score at the time of initiation of dialysis. A logistic regression analysis was used to adjust for the APACHE II score. The results of the study showed a statistically significant difference in survival (57% in patients on BCM, 46% in patients on BICM; $P = 0.03$) and in recovery of renal function (64% in patients on BICM and 43% in patients on BICM; $P = 0.001$). These differences were particularly marked in the patients who were nonoliguric (>400 ml/d of urine output) at initiation of the study. In the subset of patients who were nonoliguric at the start of dialysis, a larger fraction (70%) became oliguric after initiating dialysis on a BICM membrane, in contrast to 44% who were initiated on a BCM membrane ($P = 0.03$). It is concluded that the biocompatibility of the dialysis membrane plays a role in the outcome of patients with ARF, particularly those who are nonoliguric at the time of initiation of dialysis. (J Am Soc Nephrol 9: 257–266, 1998)

Despite many technical advances in the delivery of dialysis care over the past two decades, the mortality rate of critically ill patients with acute renal failure (ARF) requiring dialysis remains persistently high. Recently published series report a mortality rate in this patient population ranging from 42 to 88% (1–11). The increased prevalence of comorbid conditions, such as advanced age, systemic inflammatory response syndromes, multiple organ dysfunction syndromes, sepsis, and hypotension, has been shown to increase the relative risk of death (12–17).

An alternative explanation for high mortality is that the dialysis procedure itself may paradoxically prolong the course of ARF by affecting the course of recovery of renal function (18). Clinical observations suggest that in patients with ARF and modest residual renal function, the institution of dialysis often results in the development of oliguria, anuria, or both. Support for this concept comes from studies of young soldiers with trauma-induced ARF treated with hemodialysis, who were found to have fresh areas of tubular necrosis on renal histology that could not be explained by the original injuries sustained several weeks earlier (19). The possible involvement of the dialysis procedure in the prolongation of ARF is further supported by experimental studies in animals that demonstrate impaired autoregulation of renal blood flow in ARF, predisposing to repetitive episodes of renal ischemia from hypotension or hypovolemia (20–22). An earlier prospective randomized study of the effect of two different levels of dialysis intensity in patients with ARF demonstrated a trend toward increased mortality in the group of patients dialyzed more intensively, again suggesting a deleterious effect of increased exposure to dialysis (23).

A potential hypothesis to explain the adverse effects of increased exposure to dialysis, as well as the persistently high mortality rate in ARF, is that dialysis with membranes that elicit an inflammatory response upon contact with blood may adversely affect recovery by exacerbating preexisting glomerular and tubular injury (24, 25). Several studies have demonstrated that the interaction of blood with hemodialysis membranes results in reproducible degrees of complement and leukocyte activation; the intensity of these activations has been frequently used as an index of biocompatibility of the dialysis membrane (24, 25). In particular, when blood comes into contact with a polysaccharide membrane surface, such as the

Received August 14, 1996. Accepted July 24, 1997.
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1046-6673/0902-0257$03.00/0
Journal of the American Society of Nephrology

cellulose matrix of the most commonly used hemodialysis membranes, the alternative pathway of complement is activated. Intense systemic complement activation leads to the release of the anaphylotoxins C3a and C5a and also results in both granulocyte and monocyte activation, with generation and release of proinflammatory reactive oxygen species, leukotrienes, and other cytokines (25). Thus, a potential adverse effect of hemodialysis membrane bioincompatibility, particularly in ARF patients, would include development or prolongation of systemic inflammatory response syndrome, characterized by fever, hypercatabolism, leukocytosis, and worsening of tissue injury (26–28). Indeed, several experimental models in animals have demonstrated a synergistic effect of reactive oxygen species and other inflammatory mediators in prolonging ischemic ARF (29,30).

On the basis of these concepts, we initiated a prospective comparison of hemodialysis membranes with different degrees of biocompatibility (defined by their complement- and leukocyte-activating potential). Outcome parameters of the study included patient survival, recovery of renal function, development of oliguria, and duration of dialysis treatment. This study represents the combined results of a four-center trial comparing different dialysis membranes in the treatment of patients with acute renal failure, and includes the results of one center's experience, which has been published previously (31).

Materials and Methods

Study Design

All patients over 18 yr of age who were hospitalized at Vanderbilt University Medical Center, Maine Medical Center, Massachusetts General Hospital, or Iowa Methodist Medical Center and requiring hemodialysis for ARF were eligible for enrollment in this study. The study was approved by the Institutional Review Board of each institution. Exclusion criteria for this study included patients with renal transplantation and documented prior chronic renal failure (measured creatinine clearance or estimated creatinine clearance by Cockcroft–Gault formula of ≤40 ml/min). Those patients who required only ultrafiltration for treatment of fluid overload or who for specific clinical indications received continuous therapies were also excluded. No patients were excluded because of the etiology of ARF, biochemical values, or the presence of concurrent conditions. All decisions regarding the initiation and discontinuation of dialysis were made by the attending clinical nephrologists responsible for the patient's care, and in most cases did not involve the investigators of this study.

After a decision had been made to initiate hemodialysis, the patient was sequentially allocated for treatment with one of two types of dialysis membranes, which were then used for all subsequent required treatments. Eligible patients were enrolled in the order that they had presented for treatment, and the assignments to the two treatment groups were made in alternating order at each institution. After the clinical nephrologist made the decision to initiate dialysis and informed consent was obtained from the patients, the nursing staff was informed and then made the alternate membrane allocation. Once the membrane had been assigned, no attempt was made to blind either the nephrologists or the nursing staff to the membrane assignment.

This study was initiated at Vanderbilt University Medical Center in February 1991. In June 1992, the Massachusetts General Hospital began enrolling patients in the study, and in November 1992, the Maine Medical Center began enrolling patients. The Iowa Methodist Medical Center began enrolling patients in this study in March 1993. A total of 72 patients was enrolled from Vanderbilt University Hospital. These 72 patients were the subject of a previous report. Thirty-eight patients were enrolled at the Maine Medical Center, 26 patients at the Massachusetts General Hospital, and 17 patients at Iowa Methodist Medical Center. Enrollment was discontinued at Vanderbilt University Medical Center in March 1993, at Iowa Methodist Medical Center in November 1993, at the Maine Medical Center in December 1993, and at the Massachusetts General Hospital in April 1994. Enrollment in this study was stopped so the data could be analyzed in time for an American Society of Nephrology abstract deadline. All 153 patients enrolled in the study were followed until death; discharge from the hospital and off dialysis; or 3 mo after discharge from the hospital for those patients who were initially discharged from the hospital but still on dialysis.

To eliminate the possibility of confounding membrane variables, *i.e.*, flux and biocompatibility, all membranes used were low flux. Group 1 consisted of a biocompatible low-flux hemodialysis membrane. Three of the four centers used a Toray polymethylmethacrylate B2-1.5 H Filtryzer (Toray Industries, Tokyo, Japan), and one center used a low-flux polysulfone (F6, Fresenius, Bad Homburg, Germany) membrane. In all centers, the bioincompatible membrane was a low-flux cellulosic-based membrane from one of several manufacturers. (Focus 120, National Medical Care, Dublin, Ireland; TAF12, Terumo Corp., Tokyo, Japan; C121, Terumo Corp.; COBE 300, Gambro, Prittingen, Germany). All membranes used had similar hollow fiber configurations and ultrafiltration coefficients. None of the centers reused their dialyzers. All hemodialysis treatments were performed with a volumetric control machine that allowed for precise rate of fluid removal. All decisions regarding ultrafiltration rate, blood flow rate, dialysis temperature, and direction of dialysis treatment were made by the nephrologist caring for the patient. All patients used bicarbonate-based dialysate. All decisions regarding discontinuation of dialysis due to recovery of renal function were also made by the nephrologist caring for the patient, based on the recovery of renal function.

Measurement of Severity of Illness

The severity of illness in each patient was determined according to the Acute Physiology, Age, and Chronic Health Evaluation (APACHE II) score on the first day of dialysis (32, 33). This score is a sum of the scores evaluating a patient's current physiologic condition, age, and previous chronic conditions. A high APACHE II score correlates with severe acute illness and a high risk of mortality, both in the patients with (33) or without (32) acute renal failure. The utility of the APACHE II score at the time of initiation of dialysis as a measure of severity of illness and as a predictor of outcome in this study is discussed in detail in a related manuscript.

Outcome Measurements

Prospectively determined outcome measures were: survival and discharge from the hospital; the recovery of renal function (defined as the discontinuation of dialysis because it was no longer required) while in the hospital; the number of dialysis treatments given; the number of days from the first dialysis treatment to death or the recovery of renal function; and the incidence of oliguria (defined as urinary output ≤400 ml/24 h) both before and after initiation of hemodialysis treatment. It should be noted that analysis of recovery of renal function included both survivors and nonsurvivors, because some nonsurvivors recovered renal function before death. We prospectively decided to analyze all causes of mortality rather than a

specific cause of death because of the difficulty in ascertaining the cause of death in patients with multiorgan system failure. We also prospectively decided to adjust all outcome measures for the severity of illness score, as described below.

Statistical Analyses

Two methods (the unpaired *t* test and the equivalent nonparametric test, the Wilcoxon rank-sum test) were used to compare continuous variables, and Fisher's exact test was used to compare discrete variables between two groups at the start of dialysis. Differences in outcome between the two groups were assessed with Fisher's exact test. Exact logistic regression analysis, with LogXact-Turbo (Cytel Software, Cambridge, MA), was used to make an adjustment for the APACHE II score. The time from the initiation of dialysis to recovery or death was analyzed with a proportional hazards model. All analyses were two-tailed. *P* values less than 0.05 were considered statistically significant. An interim analysis of the data from one center was performed and published previously using the same protocol and statistical methods (31).

Results

Table 1 lists some of the demographic and clinical characteristics, as well as the causes of renal failure, in patients randomized to either biocompatible or bioincompatible dialyzer membranes. There were no significant differences in cause of ARF, age, gender, or race between the different treatment groups. There also were no significant differences in the percentage of intensive care unit (ICU) patients, or in the number of days from time of ICU admission to dialysis initiation between the two groups. Overall, 84% of enrolled patients were in the ICU at the time of the first dialysis treatment.

A mean ± SD of the overall APACHE II score, as well as each of its three components at the time of initiating dialysis, is included in Table 1. There were no differences either in the overall score or in any of its components at the time of initiating hemodialysis between the two treatment groups, suggesting that the clinical severity of each treatment group was similar at entry in the study. Because several studies have noted that the prognosis for patient survival is affected by the presence or absence of oliguria (12,16,17,23,33–37), we also noted the number of patients who initiated dialysis with or without oliguria. There were no significant differences by patient group in the percentage of patients who were oliguric at the initiation of hemodialysis. Similarly, serum albumin concentration, a marker of nutritional status that is now well established as a predictor of increased mortality in chronic hemodialysis patients (38–40), did not differ significantly between the two groups.

Table 2 shows the overall results for all patients in the study. Of the patients dialyzed with biocompatible membranes, 57% survived compared with a 46% survival rate in patients dialyzed with bioincompatible membranes, which was statistically significant ($P = 0.03$). The odds ratio of survival based on biocompatibility of the dialysis membrane was 2.28. (95% confidence interval [CI], 1.08 to 4.77). The percentage of

Table 1. Patient demographics and clinical characteristics at the start of hemodialysis therapy

Characteristic	Biocompatible Membrane Group ($n = 72$)	Bioincompatible Membrane Group ($n = 81$)
Age (yr)	57.3 ± 19.2	58.0 ± 17.5
Sex, no. of patients (%)		
male	49 (68%)	51 (63%)
female	23 (32%)	30 (37%)
Race, no. of patients (%)		
black	5 (7%)	5 (6%)
white	67 (93%)	74 (91%)
other	0 (0%)	2 (3%)
Cause of ARF, no. of patients (%)		
hypotension	26 (36%)	39 (48%)
drug/dye toxicity	18 (25%)	17 (21%)
sepsis	14 (19%)	15 (19%)
rhabdomyolysis	8 (11%)	9 (11%)
other	6 (8%)	1 (1%)
APACHE II score		
total score	28.1 ± 8.2	26.4 ± 7.3
acute physiologic score	23.0 ± 7.8	21.3 ± 7.4
age score	3.2 ± 2.3	3.3 ± 2.2
chronic health score	1.9 ± 2.4	1.8 ± 2.3
Oliguria, no. of patients (%)	33 (46%)	35 (43%)
Albumin (g/dl)	2.6 ± 0.7	2.7 ± 0.8

Table 2. Outcome results according to membrane group and predialysis oliguria

Group	No. of Patients (%)		*P* Value[a]
	BCM Group	BICM Group	
All patients combined	72	81	
recovery of renal function	46 (64%)	35 (43%)	0.001
survival	41 (57%)	37 (46%)	0.03
Patients nonoliguric before hemodialysis	39	46	
development of oliguria with dialysis	17 (44%)	32 (70%)	0.03
recovery of renal function	31 (79%)	21 (46%)	0.0004
survival	28 (74%)	22 (48%)	0.003
Patients oliguric before hemodialysis	33	35	
recovery of renal function	15 (45%)	14 (40%)	NS
survival	12 (36%)	15 (43%)	NS

[a] *P* values were derived from exact logistic regression after adjustment for the APACHE II score. BCM, biocompatible membrane; BICM, bioincompatible membrane.

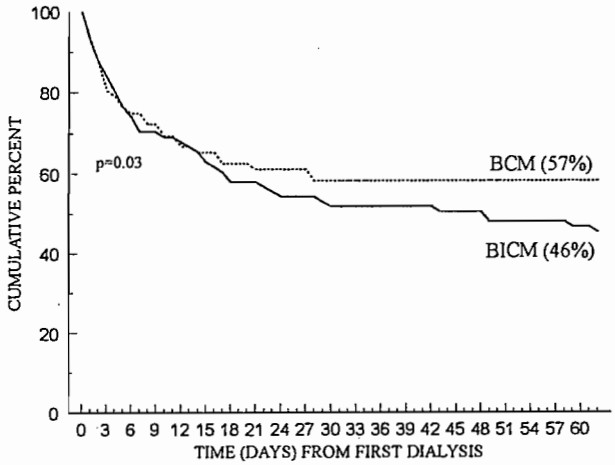

Figure 1. Survival of acute renal failure (ARF) patients by membrane group.

patients surviving over time based on randomization of the type of dialyzer membrane is presented in Figure 1.

The rate of recovery of renal function for patients dialyzed with the biocompatible membrane was 64% compared with 43% of those dialyzed using bioincompatible membranes ($P < 0.001$). The odds ratio for recovery of renal function, adjusted for APACHE II scores, was 3.47 (95% CI, 1.63 to 7.35). Some patients recovered renal function but did not survive their hospitalization. The cumulative percentage of patients recovering renal function is shown in Figure 2. There was a significantly shorter time to recovery of renal function with the use of biocompatible synthetic membranes than with cellulosic dialysis membranes ($P < 0.01$ for both the Cox proportional hazard and life table approach, and whether the time to recovery was calculated as either the number of hemodialysis treatments or "days on hemodialysis" before recovery). Thus, in the group of patients dialyzed with biocompatible membranes, there was a higher rate and a shorter interval for renal functional recovery compared with patients dialyzed with bioincompatible membranes.

Numerous studies have demonstrated that the prognosis both for renal recovery and patient survival in ARF is affected by

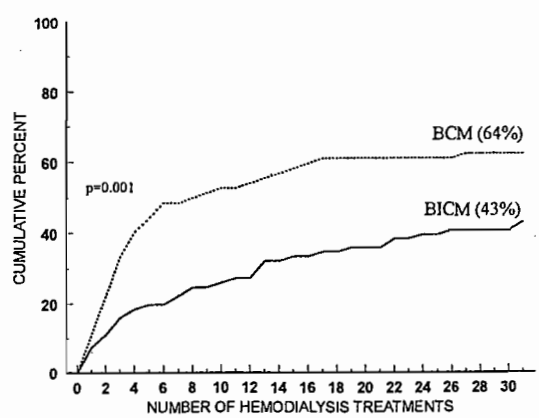

Figure 2. Renal function recovery in ARF patients by membrane group.

the presence or absence of oliguria (12,16,17,23,33–37). Because the extent of hemodynamic or toxic renal injury may differ between patients with nonoliguric and oliguric ARF (41,42), we hypothesized that the effects of hemodialyzer membrane biocompatibility might differ based on the presence or absence of oliguria. We therefore analyzed data of all patients ($n = 153$) based on the presence or absence of oliguria at the start of hemodialysis. Table 2 shows the overall results for all patients in the presence or absence of oliguria, as well as by membrane group.

The effects of the biocompatibility of the dialysis membrane were particularly evident for patients who were nonoliguric at the start of hemodialysis. Seventy-four percent of this subset of patients survived compared with 48% of those dialyzed with bioincompatible membranes ($P = 0.003$). The mean APACHE II scores at initiation of dialysis among the nonolguric patients were similar between the patients dialyzed with a biocompatible membrane (26.9 ± 8.1) compared with the patients dialyzed with a bioincompatible membrane (25.1 ± 6.8) (Table 3). Adjusting for severity of illness with the APACHE II score, the odds ratio for survival in the group dialyzed with the biocompatible membrane was 5.70 compared with the group dialyzed with the bioincompatible membrane (95% CI, 1.84 to 17.6). The median number of hemodialysis treatments before recovery in this subset of nonoliguric patients was four treatments (95% CI, 3 to 5) for those dialyzed with biocompatible membranes and 15 treatments (95% CI, 8 to 24) for those dialyzed with bioincompatible membranes ($P < 0.01$).

It is interesting to note that of patients who were initially nonoliguric at the time of initiating hemodialysis, 44% of those dialyzed with the biocompatible membrane subsequently developed oliguria, compared with 70% of those dialyzed with the bioincompatible membrane ($P = 0.03$) (Table 2). The odds ratio for developing oliguria after adjusting for APACHE II severity of illness scores by logistic regression was 0.31 (95% CI, 0.13 to 0.78); *i.e.*, nonoliguric patients initiated on dialysis with a biocompatible membrane had less than one-third the odds of developing oliguria compared with patients dialyzed with the bioincompatible membranes.

In contrast to patients who were nonoliguric at initiation of dialysis, randomization to either a biocompatible or bioincompatible membrane in oliguric patients had no effect on either patient survival or recovery of renal function (Table 2). Of the 35 patients who were oliguric at the initiation of hemodialysis and were dialyzed with bioincompatible membranes, 15 (43%) survived and 14 (40%) recovered renal function, compared

Table 3. APACHE II score at dialysis initiation: influence of membrane assignment and oliguria[a]

Group	Oliguric Patients	Nonoliguric Patients
BICM	28.0 ± 7.6	25.1 ± 6.8
BCM	29.5 ± 8.2	26.9 ± 8.1

[a] Data are presented as mean ± SD. Abbreviations as in Table 2.

with 12 of the 33 (36%) patients who were oliguric at the initiation of hemodialysis who were dialyzed with biocompatible membrane surviving and 45% of patients recovering renal function (P = NS for both recovery and survival). The mean APACHE II score at initiation of dialysis among the oliguric patients was similar between the patients dialyzed with a biocompatible membrane (29.5 ± 8.2) and the patients dialyzed with a bioincompatible membrane (28.0 ± 7.6) (Table 3). Thus, the benefits, both in patient survival and in recovery of renal function for patients hemodialyzed with biocompatible membranes compared with bioincompatible membranes, were in the subset of patients who are nonoliguric at the initiation of hemodialysis.

Although this is a multicenter prospective trial comprising the clinical results of four centers, 72 of the 153 patients (47%) came from a single institution. Therefore, we decided to analyze whether the trends observed in the largest single center were reflective of trends in the other combined centers. Table 4 represents the effect of hemodialysis membrane biocompatibility on patient survival in all patients with acute renal failure. At the largest single center (Vanderbilt University Medical Center), 57% of patients dialyzed with a biocompatible membrane survived, compared with 37% of those dialyzed with a bioincompatible membrane. The odds ratio for survival adjusted for severity of illness using the APACHE II score at the time of dialysis initiation was 2.7; however, the P value was not statistically significant at 0.069. In comparison, results at centers excluding Vanderbilt University Medical Center demonstrated a survival rate of 57% for patients dialyzed with biocompatible membranes, compared with 52% for those patients dialyzed with bioincompatible membranes. Because there was a trend toward a higher APACHE II score at the initiation of dialysis in the biocompatible group, the odds ratio for survival adjusted for severity of illness was 2.0 in favor of the use of biocompatible membranes. The P value for all centers excluding Vanderbilt University Medical Center was 0.19. When combining all centers in adjusting for severity of illness, the odds ratio for survival using a biocompatible membrane was 2.28, with a P value of 0.03.

The results of analysis of survival in subsets of patients who were nonoliguric and oliguric, respectively, at the initiation of dialysis comparing the results of Vanderbilt with the other centers are also presented in Table 4. It should be noted that in all cases, trends observed at Vanderbilt alone are also reflected in the other participating centers. For example, in patients who are nonoliguric at the time of dialysis initiation, there is a strong trend toward improved survival in patients dialyzed with a biocompatible membrane (68% *versus* 54%, adjusted odds ratio 4.2, P = 0.08) in other centers and a significant P value of 0.003 when all centers are combined. In contrast, in patients

Table 4. Analysis of survival[a]

Group	BCM	BICM	Odds Ratio	P Value
All patients				
Vanderbilt	21 (56.8%)	13 (37.1%)	2.705 (0.925 to 7.905)	0.0690
other centers	20 (57.1%)	24 (52.2%)	2.013 (0.714 to 5.676)	0.1858
combined	41 (56.9%)	37 (45.7%)	2.276 (1.085 to 4.776)	0.296
Nonoliguric patients				
Vanderbilt	16 (80.0%)	8 (40.0%)	8.639 (1.690 to 44.155)	0.0096
other centers	13 (68.4%)	14 (53.9%)	4.159 (0.836 to 20.676)	0.0816
combined	29 (74.4%)	22 (47.8%)	5.696 (1.842 to 17.610)	0.0025
Oliguric patients				
Vanderbilt	5 (29.4%)	5 (33.3%)	0.465 (0.063 to 3.425)	0.4523
other centers	7 (43.8%)	10 (50.0%)	1.051 (0.250 to 4.426)	0.9460
combined	12 (36.4%)	15 (42.9%)	0.841 (0.278 to 2.549)	0.7602

[a] Abbreviations as in Table 1.

who are oliguric at dialysis initiation (Table 4), there are no membrane-dependent trends toward an improvement either in patients at Vanderbilt University or in the other combined centers.

We also separately analyzed the recovery of renal function as a function of hemodialysis membrane biocompatibility in the Vanderbilt patients compared to the other combined centers (Table 5). In all cases, trends observed at the Vanderbilt Center are also observed in the other combined centers. Of note, the rate of recovery of renal function in all patients was significantly improved when patients were dialyzed with biocompatible membranes in both Vanderbilt alone data as well as in data of the other combined centers (both P values < 0.05), even without combining these groups, confirming the strength and consistency of the association of the recovery of renal function with the use of biocompatible dialysis membranes.

Although decisions regarding the need for the initiation of dialysis were made by the attending clinical nephrologists, we also compared biochemical variables associated with acute renal failure and urine output to see whether they differed between the two dialysis-membrane treatment groups. There were no significant differences at the initiation of hemodialysis in any of the eight measured variables (blood urea nitrogen [BUN], serum creatinine, serum bicarbonate, serum Na^+, serum K^+, pH, hematocrit, and white blood cell count) between patients dialyzed with biocompatible or bioincompatible membranes (Table 6). There also were no significant differences in urine output between the treatment groups assigned to each membrane. Because virtually all of the clinical benefit associated with dialysis using biocompatible membranes occurred in patients who are nonoliguric at the start of dialysis, we also analyzed biochemical variables associated with acute renal failure in the subgroup of patients who were nonoliguric (Table 6). There were no significant differences in BUN, potassium, creatinine, or serum bicarbonate between the nonoliguric patients dialyzed with biocompatible or bioincompatible membranes. A similar analysis of four physiologic variables (temperature, mean arterial pressure, heart rate, and respiration rate) did not demonstrate any differences between patients allocated to biocompatible or bioincompatible membranes in any patient group (data not shown). Thus, it would appear that clinical nephrologists enrolled patients into both arms of the study with very similar biochemical and physiologic perturbations and that there is no obvious bias in the initial assignment of patients to either treatment group.

Decisions regarding discontinuation of dialysis because of recovery of renal function in acute renal failure were also made by the attending clinical nephrologists. Table 7 compares four biochemical variables associated with acute renal failure at the time of discontinuation of dialysis among those patients who recovered renal function. There were no significant differences in BUN, serum creatinine, serum bicarbonate, or serum potassium levels (or urine output) between patients dialyzed with biocompatible membranes or bioincompatible membranes at the time of discontinuation of dialysis therapy. Thus, it would

Table 5. Analysis of recovery of renal function[a]

Group	BCM	BICM	Odds Ratio	P Value
All patients				
Vanderbilt	23 (62.2%)	13 (37.1%)	3.572 (1.201 to 10.627)	0.0221
other centers	23 (65.7%)	22 (47.8%)	3.370 (1.181 to 9.611)	0.0231
combined	46 (63.9%)	35 (43.2%)	3.468 (1.635 to 7.354)	0.0012
Nonoliguric patients				
Vanderbilt	17 (85%)	8 (40.0%)	17.839 (2.437 to 130.6)	0.0046
other centers	14 (73.7%)	13 (50.0%)	5.131 (1.099 to 23.956)	0.0375
combined	31 (79.5%)	21 (45.7%)	8.710 (2.616 to 29.004)	0.0004
Oliguric patients				
Vanderbilt	6 (35.3%)	5 (33.3%)	0.880 (0.165 to 4.700)	0.8813
other centers	9 (56.3%)	9 (45.0%)	2.234 (0.517 to 9.662)	0.2820
combined	15 (45.5%)	14 (40.0%)	1.515 (0.526 to 4.360)	0.4415

[a] Abbreviations as in Table 1.

Table 6. Biochemical variables at dialysis initiation[a]

Variable	BICM	BCM
All patients		
BUN (mg/dl)	97 ± 43	92 ± 47
creatinine (mg/dl)	5.9 ± 3.0	5.5 ± 2.2
Na^+ (mEq/L)	135 ± 7	137 ± 9
HCO_3^- (mEq/L)	20 ± 6	20 ± 6
K^+ (mEq/L)	4.8 ± 1.1	4.7 ± 1.3
pH	7.33 ± 0.12	7.32 ± 0.14
HCT (vol %)	28.2 ± 6.1	28.0 ± 5.4
WBC ($\times 10^6$)	15.4 ± 10.3	14.9 ± 8.2
Nonoliguric patients		
BUN (mg/dl)	106 ± 45	94 ± 54
creatinine (mg/dl)	5.9 ± 3.0	5.2 ± 2.2
Na^+ (mEq/L)	136 ± 8	137 ± 10
HCO_3^- (mEq/L)	21 ± 6	20 ± 5
K^+ (mEq/L)	4.6 ± 0.9	4.6 ± 1.4
pH	7.36 ± 0.10	7.32 ± 0.13
HCT (vol %)	28.5 ± 5.0	28.2 ± 6.5
WBC ($\times 10^6$)	14.1 ± 9.8	13.9 ± 7.7
urine output (ml/24 h)	1547 ± 1150	1256 ± 1064
Oliguric patients		
BUN (mg/dl)	85 ± 39	90 ± 36
creatinine (mg/dl)	5.9 ± 3.1	5.9 ± 2.1
Na^+ (mEq/L)	135 ± 7	137 ± 8
HCO_3^- (mEq/L)	20 ± 5	19 ± 6
K^+ (mEq/L)	5.2 ± 1.2	4.9 ± 1.2
pH	7.31 ± 0.13	7.32 ± 0.15
HCT (vol %)	27.8 ± 7.3	27.6 ± 3.6
WBC ($\times 10^6$)	17.1 ± 10.9	16.1 ± 8.8

[a] All data are presented as mean ± SD. There were no statistical differences between patients randomized to biocompatible or bioincompatible membranes. BUN, blood urea nitrogen; HCT, hematocrit; WBC, white blood cell count. Other abbreviations as in Table 2.

Table 7. Biochemical variables at dialysis discontinuation: all patients[a]

Variable	BICM	BCM
BUN (mg/dl)	68 ± 39	70 ± 32
Creatinine (mg/dl)	4.3 ± 2.3	4.2 ± 2.1
HCO_3^- (mEq/L)	25 ± 3	25 ± 4
K^+ (mEq/L)	3.8 ± 0.4	3.9 ± 0.6
Urine output (ml/24 h)	1356 ± 1047	1903 ± 1796

[a] All data are presented as mean ± SD. There were no statistical differences between patients randomized to BCM or BICM membranes. Abbreviations as in Tables 2 and 6.

appear that clinical nephrologists used similar standards for evaluating recovery of renal function in both arms of this study.

Discussion

In this study, 153 patients who developed ARF requiring hemodialysis were prospectively alternatively allocated to dialysis treatments with either a biocompatible or bioincompatible membrane. The results of this study demonstrate that patients with ARF who were dialyzed with biocompatible membranes were more likely to recover renal function and had a significantly lower mortality than those dialyzed with bioincompatible membranes, and were less likely to develop oliguria than those dialyzed with bioincompatible membranes.

Of interest, all of the advantages seen in patient survival and recovery of renal function with the use of biocompatible membranes were confined to the subset of patients who were nonoliguric at the initiation of hemodialysis. In this subset of patients, there was a more notable overall reduction in mortality and improvement in recovery of renal function for those dialyzed on a biocompatible synthetic membrane compared with those dialyzed on a bioincompatible unmodified cellulosic membrane. In contrast, in the subset of patients who were oliguric at the initiation of hemodialysis, there was no difference in patient survival or recovery of renal function for those dialyzed with a biocompatible *versus* a bioincompatible membrane.

The difference in the effect of membrane biocompatibility in patients with or without oliguria at the onset of dialysis is consistent with the hypothesis that the adverse effects seen with bioincompatible membranes are due to the production of proinflammatory substances, including complement anaphylotoxins; reactive oxygen and nitrogen species; cytokines; and leukotrienes. Prolongation of uncontrolled systemic inflammatory response can lead to development of multiorgan dysfunction syndrome. Both clinical entities are known to substantially increase patient mortality in the ICU setting (26). Additionally, the inflammatory consequences associated with hemodialysis membrane bioincompatibility could affect the renal microcirculation, thereby exacerbating both glomerular and tubular injury and prolonging the course of acute renal failure. These substances are both vasoconstrictive and potentially damaging to host tissue. In several animal models, renal blood flow is higher in injuries associated with nonoliguric acute renal failure (43). Thus, it is likely that the renal microcirculation will be exposed to a higher concentration of complement and neutrophil activation products in this group of patients.

An interesting feature of this study is that the use of biocompatible hemodialysis membranes had an earlier and greater impact on the percentage of patients who recover renal function than on patient survival. This is not an unexpected finding given the severity of comorbid conditions, including multiorgan system failure, that frequently accompany critically ill patients with acute renal failure. The effects of hemodialysis membrane biocompatibility on recovery of renal function would be noticeable almost immediately, with a divergence in the rates of recovery of renal function appearing within several days of enrollment in the study (Figure 2). Another possible explanation for this discrepancy is that the effects of ongoing uremia in patients who do not recover renal function have a

cumulative or progressive effect on other comorbidities, ultimately leading to a decrease in patient survival. Finally, it is possible that the continued need for dialysis has ongoing deleterious effects, including risks of bleeding, hypotension, or infection. All such explanations, however, are at best speculative at present.

The assessment of the severity of illness was performed by using the APACHE II score at the time of initiation of dialysis, since in many cases, the interval between the diagnosis of ARF and the initiation of dialysis was brief. Although several other measures of severity of illness have been proposed, including sequential measurements of APACHE II and APACHE III, recent data suggest that the index used in this study is representative (44). A further discussion of the validity and usefulness of the APACHE II score at dialysis initiation is the subject of a separate manuscript in preparation.

There have been two recently published reports comparing the outcome in patients with ARF undergoing hemodialysis with unmodified dialysis membranes compared with more biocompatible synthetic membranes. Both of these studies were results of single-center experiences. Schiffl *et al.* compared the results of dialysis with cellulosic membranes to polyacrylonitrile (PAN) membranes and demonstrated a lower survival rate (38%) in patients dialyzed with bioincompatible membranes *versus* the more biocompatible PAN membranes (65%) (45).

In contrast to our study, the PAN dialysis membrane differs from the typical unmodified cellulosic membrane both in terms of biocompatibility (complement and granulocyte activation) and in terms of urea clearance and ultrafiltration coefficient, because the PAN membrane is high flux. PAN membranes also have important adsorptive properties that also may contribute to improved biocompatibility (46). In that study, the rate of mortality, particularly from sepsis, was reduced by more than half in the group of patients dialyzed with PAN membranes compared with those dialyzed with the unmodified cellulosic membranes. The improvement in patient survival in that study compared with our study may represent additive benefits from the high-flux characteristics of the PAN membrane.

Kurtal *et al.* published a brief report comparing dialysis with a bioincompatible unmodified cellulosic membrane with a more biocompatible polyamide membrane (47). In a study of 62 patients, they did not observe a difference in patient and percentage of patient survival or in the rate of recovery of renal function based on the type of membrane chosen. There are several noticeable differences between the study by Kurtal *et al.* and the present study. In the study by Kurtal, although APACHE II scores were similar between the biocompatible and bioincompatible membrane groups, the causes of ARF were not. For example, 40% of the patients dialyzed with the biocompatible membrane had ARF secondary to hypotension *versus* 22% in the bioincompatible group. Drug-induced ARF was more common in the bioincompatible group (22%) than in the biocompatible group (12%). Several studies have emphasized that drug-induced ARF has a relatively good prognosis, whereas hypotension-induced ARF has a relatively poor prognosis. In addition, patients in the study by Kurtal *et al.* had lower mean APACHE II scores than our study, and overall survival for all patients was excellent at 68%, which would make it difficult to detect small differences. This brief report did not examine results in subsets of oliguric or nonoliguric patients. Hemodialysis was also initiated at higher levels of BUN than in the present study.

Although the results of the present study strongly suggest that the use of biocompatible membranes is associated with a better clinical outcome for patients with acute renal failure, there are several weaknesses in the study design that must be considered. First, we did not perform an intention to treat analysis. Of the 171 patients initially enrolled in the study, 18 were excluded before any analysis of the data when it was retrospectively determined that they met patient exclusion criteria (14 patients) or because of violations of the study protocol after dialysis was initiated (two patients were inadvertently dialyzed on the wrong dialysis membrane on at least one occasion, and one patient received continuous renal replacement therapy). In addition, a single patient who was randomized to the study recovered renal function without receiving dialysis therapy. Although the lack of an intention to treat analysis is a weakness of this study, it is unlikely to have had a significant effect on the results.

A second potential weakness of this study is the lack of a blinded randomization procedure. Instead of a blinded but very cumbersome randomization procedure, patients were allocated on a consecutive basis at each center to either biocompatible or bioincompatible dialysis membranes. This study design in theory could be subject to observer bias on the part of clinical nephrologists enrolling patients in the study. Despite this weakness in the study design, several lines of evidence would suggest that this did not result in significant bias in patient enrollment. First, in the majority of cases, decisions regarding the initiation of dialysis and enrollment in the study were made by attending clinical nephrologists other than the investigators of this study. Second, the clinical nephrologist making the decision to initiate dialysis and enroll the patient in the study then contacted the dialysis nursing staff, who subsequently made the alternate membrane allocation. Additionally, biochemical variables associated with acute renal failure (Figure 5), nutritional parameters as measured by serum albumin, and APACHE II scores at the initiation of dialysis (Table 1) did not differ between the membrane assignment groups, suggesting that there was little, if any, bias in patient membrane allocation. Finally, it should be noted that although this study design was not ideal, similar alternate allocations by these designs have been used in most previously published, peer-reviewed comparisons of dialysis membranes in acute renal failure (45,47).

A third weakness of the present study is that an interim analysis of one center's experience has been published previously. Indeed, the lead center for this study began enrolling patients before the other centers, and results from the initial 40 patients enrolled at that center were published in abstract form before the completion of enrollment at all four centers, potentially introducing bias in the results of the other centers. It should be noted, however, that all centers discontinued enrollment at approximately the same time and that no further

interim analysis of the data from the four centers was made until all four centers had discontinued enrolling further patients. Furthermore, an analysis of the data in this multicenter trial does not show a significant center effect. Because of this potential weakness in the study, we have separately reported the results from Vanderbilt compared with the other three centers and demonstrated a similar effect of dialysis membrane biocompatibility on patient outcome when adjusted for severity of illness.

A fourth potential weakness of the study is that we did not measure the intensity of dose of delivered dialysis (such as with urea kinetic modeling) on patient outcome. At the time that this study was conceived and conducted, there was minimal, if any, clinical data suggesting that the dose of delivered dialysis could affect patient outcome in acute renal failure. We did, however, choose hemodialysis membrane assignments to have similar surface area, ultrafiltration coefficients, low and middle molecular weight solute clearance characteristics, and hollow fiber configurations. Because the major difference between the two membrane assignment groups is the complement- and leukocyte-activating potential of the dialyzer membranes, this likely accounts for the differences between the two groups in patient survival and recovery of renal function.

It should also be noted that in this study we compare the outcomes of patients with acute renal failure dialyzed either with unmodified cellulosic dialysis membranes with high complement- and leukocyte-activating potential or with synthetic dialyzer membranes with substantially lower (at least one order of magnitude) complement- and leukocyte-activating potential. A recent U.S. Renal Data System cohort study in end-stage renal disease has suggested that modifications of cellulosic membranes that diminish their complement-activating potential may result in enhanced patient survival (similar to synthetic membranes) compared with patients dialyzed with unmodified cellulosic membranes. Thus, the results of this study, which demonstrate improved outcomes in patients with acute renal failure dialyzed with synthetic *versus* unmodified cellulosic dialysis membranes, may or may not be applicable to substituted cellulosic membranes.

In summary, in this multicenter prospective study of patients with acute renal failure, the biocompatibility of the dialysis membrane was found to be important in determining patient survival, recovery of renal function, and the likelihood of developing oliguria. Biocompatible membranes should be used when available in patients with acute renal failure, particularly in those patients who are nonoliguric when dialysis initiation is required.

Acknowledgments

The authors gratefully acknowledge the assistance of their nursing collaborators: Susan Smith (Maine Medical Center), Angela Del Vecchio (Massachusetts General Hospital), and Barbara Schnoor (Iowa Methodist Medical Center). This study was supported by National Institutes of Health Grant R01-HL36015-05. Maine Medical Center acknowledges a small grant for partial support of a research coordinator from Toray Industries (Tokyo, Japan).

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