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# EFFECT OF THE DIALYSIS MEMBRANE IN THE TREATMENT OF PATIENTS WITH ACUTE RENAL FAILURE

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**Abstract** *Background.* The mortality rate among patients with acute renal failure remains high, and the role of the biocompatibility of the dialysis membrane in the resolution of this disorder is not known.

*Methods.* We prospectively studied 72 patients with acute renal failure who required hemodialysis and assigned them to two treatment groups. One group underwent dialysis with the widely used cuprophane dialysis membrane, which activates the complement system and leukocytes, and the other group underwent dialysis with a synthetic polymethyl methacrylate membrane, which has a more limited effect on complement and leukocytes. Scores on the Acute Physiology, Age, and Chronic Health Evaluation (APACHE II) were calculated at the initiation of dialysis. Survival and the recovery of renal function were determined with the use of proportional-hazards and exact logistic-regression analyses.

*Results.* When dialysis was initiated, the patients in the two groups were similar in terms of age, APACHE II scores, the prevalence of oliguria, and biochemical indexes of renal failure. Twenty-three of the 37 patients (62 percent) in the group undergoing dialysis with the polymethyl methacrylate membrane recovered renal function, as compared with 13 of the 35 patients (37 percent) in the group undergoing dialysis with the cuprophane membrane ($P = 0.04$ after adjustment for the APACHE II score). The median number of dialysis treatments required before the recovery of renal function was 5 in the former group and 17 in the latter group ($P = 0.02$). Twenty-one patients (57 percent) undergoing dialysis with the polymethyl methacrylate membrane survived, as compared with 13 patients (37 percent) undergoing dialysis with the cuprophane membrane ($P = 0.11$). Of the 20 patients in each group who initially had nonoliguric acute renal failure, the survival rates were 80 percent with the polymethyl methacrylate membrane and 40 percent with the cuprophane membrane ($P = 0.01$).

*Conclusions.* Among patients with acute renal failure requiring hemodialysis, the use of the polymethyl methacrylate membrane, as compared with the cuprophane membrane, resulted in improved recovery of renal function. (N Engl J Med 1994;331:1338-42.)

THE mortality rate among patients with acute renal failure remains high, ranging from 42 to 75 percent, despite numerous advances in the diagnosis and treatment of this disorder.[1-4] Several concurrent conditions, such as coma or dependence on a respirator, increase the risk of death in patients with acute renal failure, and the high prevalence of these conditions may explain the persistently high mortality rate.[5]

The mortality rate is higher among patients with acute renal failure who undergo hemodialysis than among those who do not need such treatment.[6-9] Different methods of dialysis and the biocompatibility of the dialysis membrane — defined as the extent of complement and neutrophil activation — influence the effectiveness of the treatment.[10] Recent studies in animals indicate that the recovery from acute renal failure is influenced by the degree of leukocyte infiltration in the kidney and by the complement-activating potential of the dialysis membrane to which the animal is exposed.[11-13]

We undertook a prospective comparison of the influence of dialysis membranes with different degrees of biocompatibility on the recovery of renal function and survival in patients with acute renal failure requiring hemodialysis. We used two membranes: a cellulose membrane made from cotton fibers (cuprophane) that is widely used in the treatment of renal failure and is known to activate complement and neutrophils, and a synthetic membrane (polymethyl methacrylate) associated with more limited complement and neutrophil activation.

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## METHODS

### Study Design

All patients over 18 years of age who were hospitalized at Vanderbilt University Medical Center and required hemodialysis for acute renal failure were eligible for enrollment in the study. The study was approved by the institutional review board, and informed consent was obtained from the patients or their next of kin. Patients were excluded from the study if they had undergone renal transplantation or had documented prior chronic renal failure or if they required only ultrafiltration for fluid overload. No patients were excluded on the basis of the cause of acute renal failure, biochemical values, or the presence of concurrent conditions. All decisions regarding the initiation and discontinuation of dialysis were made by the attending nephrologists without consultation with the investigators or knowledge of the membrane to be used.

Once a decision had been made to initiate hemodialysis, the patient was assigned to treatment with one of the two types of membranes, which was then used for all subsequent dialysis treatments. All 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. We used a polymethyl methacrylate membrane (Toray B2-1.5H Filtryzer, Toray Industries, Tokyo, Japan) as the biocompatible membrane and a cuprophane membrane (F-120, National Medical Care, Rockleigh, N.J.) as the bioincompatible membrane. The two membranes have hollow fibers and similar clearance and ultrafiltration characteristics, with an ultrafiltration coefficient under 5 ml per millimeter of mercury per hour. Both membranes have been approved by the Food and Drug Administration and are available commercially. The membranes were not reused. The polymethyl methacrylate membrane costs approximately $25, and the cuprophane dialyzer costs $11. All treatments were performed with a volumetric-control machine that allowed precise ultrafiltration.

### Patients' Characteristics

A total of 83 patients requiring hemodialysis were enrolled in the study. Nine patients were excluded after they had been assigned to a treatment group because they did not have acute renal failure. Two of these patients were excluded because of the institution of contin-

uous therapy for fluid overload, two had documented prior chronic renal failure, and five required only ultrafiltration for fluid overload. Two other patients underwent dialysis with the wrong membrane on at least one occasion through inadvertent errors. These two patients were also excluded from the study. All 11 patients were excluded before their outcome was known and before the results were analyzed.

### Measurement of Severity of Illness

The severity of illness in each patient was determined according to the score on the Acute Physiology, Age, and Chronic Health Evaluation (APACHE II)[14] on the first day of dialysis. This score is the sum of the scores for the patient's current physiologic condition, age, and previous chronic conditions. The current-physiology score measures the degree of acute illness and is the sum of the scores assigned to the most abnormal physiologic values for each of 12 variables: temperature, mean arterial pressure, heart rate, respiratory rate, oxygenation, arterial pH, serum sodium, serum potassium, serum creatinine, hematocrit, white-cell count, and score on the Glasgow Coma Scale. Summed together, these three components (current-physiology score, age points, and chronic-conditions score) give a total APACHE II score ranging from 0 to 71. A high APACHE score correlates with severe acute illness and a high risk of mortality.[14-16]

### Outcome Measurements

Outcome measures included survival, the recovery of renal function (defined as the discontinuation of dialysis because it was no longer required), 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 per 24 hours) both before and during hemodialysis.

### Statistical Analysis

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 the two groups at the start of treatment with dialysis.

Differences in outcome between the two groups were assessed with Fisher's exact test. An exact logistic-regression analysis, performed with LogXact-Turbo (Cytel Software, Cambridge, Mass.), 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 to indicate statistical significance.

An interim analysis of the data was performed after 40 patients had been enrolled, for presentation at a conference. No other interim analyses were performed. The interim and final analyses were performed with the same statistical methods.

## Results

The demographic and clinical characteristics of the patients and the primary causes of their renal failure are shown in Table 1. There were no significant differences between the two groups in terms of age, sex, race, or cause of acute renal failure. There were also no significant differences in the initial APACHE II score or any of its components, the presence of oliguria (a known indicator of a poor prognosis),[3,5,9,17,18] or biochemical and nutritional values[19] at the initiation of dialysis.

The outcome is shown in Table 2 according to the type of membrane used for dialysis and the presence or absence of oliguria at the initiation of dialysis. Of the 37 patients undergoing dialysis with the polymethyl methacrylate (biocompatible) membrane, 23 (62 percent) recovered renal function, as compared with 13 (37 percent) of the 35 patients who underwent dialysis with the cuprophane (bioincompatible) membrane (P = 0.04 after adjustment for the baseline APACHE II score; P = 0.06 before adjustment). The odds ratio for the recovery of renal function with the polymethyl methacrylate membrane, as compared with the cuprophane membrane, was 3.5 (95 percent confidence interval, 1.1 to 12.4).

After adjustment for the APACHE II score with

Table 1. Characteristics of the Patients at the Time of Initiation of Hemodialysis.*

| Characteristic | Polymethyl Methacrylate Membrane (N = 37) | Cuprophane Membrane (N = 35) |
|---|---|---|
| Age — yr | 50±18 | 52±19 |
| Sex — no. of patients (%) | | |
| Male | 29 (78) | 22 (63) |
| Female | 8 (22) | 13 (37) |
| Cause of acute renal failure — no. of patients (%) | | |
| Hypotension | 13 (35) | 14 (40) |
| Sepsis | 6 (16) | 6 (17) |
| Drugs | 8 (22) | 9 (26) |
| Rhabdomyolysis | 7 (19) | 5 (14) |
| Other | 3 (8) | 1 (3) |
| APACHE II score | 29±9 | 29±8 |
| Current physiologic condition | 25±8 | 24±8 |
| Age | 2±2 | 3±2 |
| Previous chronic conditions | 2±2 | 2±2 |
| Oliguria — no. of patients (%) | 17 (46) | 15 (43) |
| Biochemical values | | |
| Blood urea nitrogen — mg/dl | 90±55 | 93±41 |
| Serum creatinine — mg/dl | 5.4±2.4 | 5.0±2.9 |
| Arterial pH | 7.3±0.2 | 7.3±0.1 |
| Arterial $PO_2$ — mm Hg | 79±19 | 77±20 |
| Serum potassium — mmol/liter | 5.1±1.3 | 4.7±1.2 |
| White-cell count — cells/mm$^3$ | 13.5±8.0 | 14.1±11.9 |
| Serum albumin — g/dl | 2.6±0.7 | 2.8±0.8 |

*There were no significant differences between the two groups. Plus–minus values are means ±SD. $PO_2$ denotes partial pressure of oxygen. To convert values for blood urea nitrogen to millimoles per liter, multiply by 0.357; to convert values for serum creatinine to micromoles per liter, multiply by 88.4.

Table 2. Outcomes of Hemodialysis in Patients with Acute Renal Failure, According to the Type of Membrane Used.*

| Outcome | Polymethyl Methacrylate Membrane | Cuprophane Membrane | P Value* |
|---|---|---|---|
| | *no. of patients (%)* | | |
| All patients combined | 37 | 35 | |
| Recovery of renal function | 23 (62) | 13 (37) | 0.04 |
| Survival | 21 (57) | 13 (37) | 0.11 |
| Patients without oliguria before hemodialysis | 20 | 20 | |
| Development of oliguria during hemodialysis | 8 (40) | 15 (75) | 0.047 |
| Recovery of renal function | 17 (85) | 8 (40) | 0.003 |
| Survival | 16 (80) | 8 (40) | 0.01 |
| Patients with oliguria before hemodialysis | 17 | 15 | |
| Recovery of renal function | 6 (35) | 5 (33) | 1.0 |
| Survival | 5 (29) | 5 (33) | 0.83 |

*P values were derived from an exact logistic regression after adjustment for the APACHE II score.

proportional-hazards regression analysis, the time from the initiation of dialysis to the recovery of renal function was significantly shorter among the patients undergoing dialysis with the polymethyl methacrylate membrane than among those undergoing dialysis with the cuprophane membrane, in terms of both the number of hemodialysis treatments (Fig. 1) and the duration of hemodialysis ($P = 0.02$ for both). The median number of dialysis treatments needed for the recovery of renal function was 5 (duration, 11 days) among the patients undergoing dialysis with the polymethyl methacrylate membrane and 17 (duration, 33 days) among those undergoing dialysis with the cuprophane membrane.

Twenty-one patients (57 percent) in the group undergoing dialysis with the polymethyl methacrylate membrane survived, as compared with 13 (37 percent) in the group undergoing dialysis with the cuprophane membrane ($P = 0.11$) (Table 2, Fig. 2). Patients in the former group survived longer after the start of dialysis (median survival, >84 vs. 22 days) ($P = 0.3$).

Forty patients (20 in each group) had nonoliguric acute renal failure at the time dialysis was initiated. Oliguria developed in 15 of the 20 patients (75 percent) undergoing dialysis with the cuprophane membrane and in 8 (40 percent) of those undergoing dialysis with the polymethyl methacrylate membrane ($P = 0.047$ after adjustment for the APACHE II score). In the group of patients who did not have oliguria before dialysis, the patients undergoing dialysis with the polymethyl methacrylate membrane did better than those undergoing dialysis with the cuprophane membrane, with respect to the recovery of renal function ($P = 0.003$), survival ($P = 0.01$), and the median number of dialysis treatments needed for recovery (3 vs. 17 treatments, $P<0.05$). Among the patients who had oliguria before the initiation of dialysis, the recovery of renal function and survival did not differ significantly between the two treatment groups.

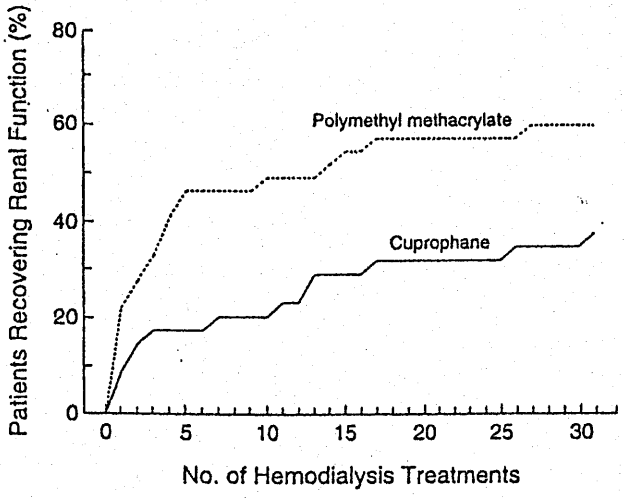


Figure 1. Recovery of Renal Function in Patients with Acute Renal Failure Undergoing Dialysis with a Polymethyl Methacrylate or Cuprophane Membrane, According to the Number of Hemodialysis Treatments.

Not shown on the graph are the results for one patient in the group undergoing dialysis with the polymethyl methacrylate membrane, who recovered renal function after 72 treatments.

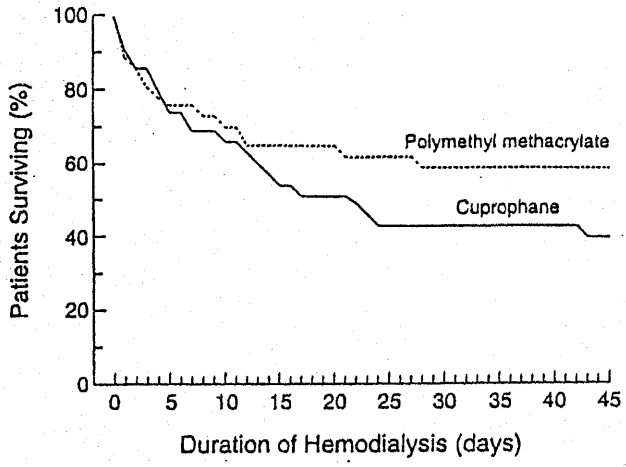


Figure 2. Survival of Patients with Acute Renal Failure Undergoing Dialysis with a Polymethyl Methacrylate or Cuprophane Membrane.

Not shown on the graph are the results for one patient in the group undergoing dialysis with the polymethyl methacrylate membrane, who died after 84 days, and one patient in the group undergoing dialysis with the cuprophane membrane, who died after 61 days.

Hypotension, defined as a decrease in mean arterial pressure of at least 20 mm Hg, occurred at least once during 30 percent of the treatments with the polymethyl methacrylate membrane and during 28 percent of those with the cuprophane membrane ($P = 0.46$).

Among the patients who recovered renal function, the mean (±SD) interval between the last session of dialysis and discharge or death was 26±25 days for those undergoing dialysis with the polymethyl methacrylate membrane and 21±17 days for those undergoing dialysis with the cuprophane membrane ($P = 0.72$). None of the patients who recovered renal function required a reinitiation of dialysis.

## Discussion

These results suggest that the use of a biocompatible dialysis membrane (polymethyl methacrylate) increased the likelihood that renal function would recover and resulted in some improvement in the survival of patients with acute renal failure. These effects were particularly evident in the patients who did not have oliguria at the start of hemodialysis.

A role for the effect of the biocompatibility of the dialysis membrane on the outcome of dialysis is supported by several studies of the role of activated neutrophils in animals with acute renal injury. These studies have shown the adverse effects of infiltrating leukocytes on the recovery of renal function[12,13,20] and on the whole-kidney glomerular filtration rate when

activated neutrophils are infused into a mildly ischemic kidney.[21] In studies of rats with acute renal failure, we found that dialysis with a membrane that activated complement and neutrophils led to a slower resolution of renal failure and was associated with a threefold increase in the number of neutrophils per glomerulus in histologic sections, as compared with the results of dialysis with a membrane that did not activate complement.[11]

A recently published report compares the outcome in two groups of patients with acute renal failure, one undergoing dialysis with a cuprophane membrane and the other with a polyacrylonitrile (biocompatible, high-flux) membrane.[22] The rate of mortality, particularly from sepsis, and the course of renal dysfunction were less severe in the group undergoing dialysis with the polyacrylonitrile membrane. However, it is not clear whether this difference in outcome was due to a difference in the flux or the biocompatibility of the two membranes used. The results of our study point to the importance of the biocompatibility of the dialysis membrane.

The activation of complement and neutrophils and the delay in the recovery of renal function can occur through several pathways.[10] Complement-activation products have direct and indirect vasoconstrictive properties.[23] In addition, activated neutrophils secrete several vasoconstrictive compounds that can exacerbate ischemia, particularly in the medullary region of the kidney, which is especially susceptible to ischemic insults because of the low oxygen tension in that region.[24,25] The products of activated complement, as well as those of activated neutrophils, may interact with glomerular endothelial cells and lead to inhibited secretion of the endothelium-derived relaxing factor nitric oxide.[26] In addition, reactive oxygen radicals, also products of neutrophil activation, have deleterious effects on tubular and glomerular cells.[27] A recent study documented the release of reactive oxygen radicals during dialysis with complement-activating membranes but not with a non–complement-activating membrane.[28]

The difference in effect of the biocompatibility of the dialysis membrane according to the presence or absence of oliguria in patients with acute renal failure is also consistent with this proposed pathophysiologic process. Renal blood flow is generally higher in patients with nonoliguric acute renal failure,[29] and their kidneys are likely to be perfused with higher concentrations of complement- and neutrophil-activation products.

It has been suggested that dialysis itself may prolong the course of acute renal failure.[30] The proposed pathophysiologic basis of this effect is the lack of autoregulation of blood flow to the ischemic kidney, so that hypotension, which is sometimes induced during dialysis, results in further ischemia.[31] In our study, however, the frequency of hypotension during dialysis was low and similar in the two patient groups. Nevertheless, the occurrence of hypotension and the activation of complement and neutrophils by a specific dialysis membrane are not mutually exclusive and may be additive phenomena.[32]

In summary, the biocompatibility of the dialysis membrane may be an important factor in the recovery from acute renal failure, particularly among patients without oliguria at the initiation of dialysis. The use of a biocompatible membrane may also slow the rate of loss of residual renal function in patients undergoing long-term hemodialysis.[33] Although the biocompatible membrane we used costs more than the cuprophane membrane, the difference is marginal as compared with the difference in the total cost of treatment.

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