J Am Soc Nephrol 9: 2153–2156, 1998

Dialyzer Reuse and the Treatment of Patients with End-Stage Renal Disease by Hemodialysis

PAUL L. KIMMEL and GARY J. MISHKIN

Division of Renal Diseases and Hypertension, Department of Medicine, George Washington University Medical Center, Washington, DC.

The reuse of dialyzers has been a concern of nephrologists for almost two decades (1–3), since its development more than 35 years ago (4). Early, small studies, often but not universally based within one unit, suggested that reuse of dialyzers was safe, but that treatment and patient characteristics such as clearance, biocompatibility, and host responses had to be monitored (5–8). The potential harmful role of hemolysis (9) and the possibility that patients would develop maladaptive immune responses associated with reuse had been raised (10,11). Clinical concern was rather centered on the "first-use" phenomenon associated with the use of Cuprophan dialyzers: leukopenia, hypoxemia, and complement activation that were occasionally associated with severe hemodynamic instability and anaphylactic manifestations (12). Indeed, some studies suggested that the reuse of dialyzers might be advantageous (13), perhaps by diminishing the leukopenia associated with the initial phase of hemodialytic treatment (14–17).

As dialysis programs expanded and were included in national for-profit chains and fiscal efficiency was sought, reuse of dialyzers became increasingly economically attractive and a fiscal necessity. In 1996 only 19.5% of dialysis units did not reuse dialyzers, compared with 31.7% in 1989 (18). This trend has occurred pari passu with the advent of the widespread use of erythropoietin to treat the anemia of renal disease (19), the disappearance of acetate-based dialysate, the increased use of synthetic dialyzers, and a decrease in mortality in the U.S. ESRD program (20). More recently, evidence has accumulated suggesting that the use of synthetic dialyzers is associated with improved outcome in patients with ESRD treated with hemodialysis (21,22). The higher cost of these dialyzers, especially when used in innovative techniques such as double high-flux hemodiafiltration (23,24), has mandated reuse of dialyzers, given the level of fixed reimbursements for hemodialytic treatments in the United States.

As the use of synthetic dialyzers has increased dramatically in the United States, so has the prevalence of reuse (18). Reuse patterns, tracked in the Dialysis Morbidity and Mortality Study, differ across the country (18), and centers reusing have a higher proportion of patients treated with synthetic dialyzers, with higher serum albumin concentrations and a tendency to higher Kt/V values (Lawrence Y. C. Agodoa, National Institutes of Health, Division of Kidney, Urologic and Hematologic Diseases, personal communication). Reuse is most prevalent in free-standing for-profit units and least commonly encountered in hospital-based units. Formaldehyde was the most commonly used germicide in 1989, but by 1996, a mixture of peracetic acid and hydrogen peroxide (Renalin®) had become the predominant sterilant in reuse procedures (18,20). Peracetic acid mixture is the most often used germicide in hospital facilities, but an approximately equal number of free-standing for-profit units use peracetic acid- and formaldehyde-based sterilant techniques. Formaldehyde is currently the most common sterilant used when reuse techniques are manual (58%) (Lawrence Y. C. Agodoa, personal communication). The use of automatic peracetic acid reprocessing techniques increased from 1989 to 1996, whereas the use of formaldehyde-based automatic techniques decreased. The number of reuses does not vary according to the sterilant processes employed in the United States (Lawrence Y. C. Agodoa, personal communication). However, the safety of the germicides used in the sterilization processes critical to reuse, and whether there are risks associated with the type of sterilant used have been a current concern of caretakers and policy-makers.

Held, Pauly, and Diamond, in a study of a subset of 4661 incident patients who started treatment with hemodialysis in 1977, demonstrated a decreased risk of death in patients who were treated with reused dialyzers processed with formaldehyde (25). Held *et al.*, in a study of 3261 patients who started treatment with hemodialysis in 1986 and 1987, were unable to detect significant differences in mortality between groups of patients treated with different germicides, using a proportional hazards analysis employing 37 covariates (26). The conclusions were limited by the relatively small sample size. However, a trend toward increased mortality risk was noted in the group of patients treated with dialyzers manually reprocessed with peracetic acid (26). These findings prompted the follow-up studies described below.

In 1994 Held *et al.*, in a point-prevalent study of 66,097 ESRD patients never transplanted and treated with conventional hemodialysis in free-standing units in 1989 and 1990, found that patients in dialysis units that disinfected dialyzers with a peracetic acid/hydrogen peroxide/acetic acid mixture or glutaraldehyde had higher mortality than patients treated in dialysis units that did not reuse dialyzers (relative risks: 1.13, $P < 0.001$; 1.17, $P = 0.01$); (27). There was no difference

1046-6673/09011-2153$03.00/0
Journal of the American Society of Nephrology
Copyright © 1998 by the American Society of Nephrology

demonstrated in mortality risk between patients treated in dialysis units that disinfected dialyzers using formaldhyde and patients treated in units that did not reuse (relative risk 1.06, $P = 0.088$) or related to specific mode of reprocessing technique (automatic *versus* manual). The findings were similar for patient- and unit-level analyses, but probability values and confidence intervals were shown only for unit-level analyses. Preliminary analyses suggested that patients treated with reused high-flux dialyzers had a lower or similar mortality to those treated in dialysis units using conventional dialysis techniques, not reusing dialyzers. Additional, preliminary analyses suggested that patients treated in hospital-based dialysis units that reused dialyzers with peracetic acid had lower mortality than those in units using glutaraldehyde or formaldehyde. This study did not control for patient comorbidity except for cause of renal failure., *i.e.*, diabetes mellitus. Dialysis unit characteristics such as free-standing *versus* hospital status were only addressed in preliminary analyses. The effect of profit *versus* nonprofit status of units was not addressed.

Luehmann and Cosentino, of the Minntech Corp., in a reanalysis of the data, vigorously refuted these findings on analytic grounds and because they believed the USRDS study was "inaccurate with regard to both the number and identity (ownership status) of Renalin® manual-reprocessing facilities" (28). They stated that "the absence of detailed information concerning delivered therapy is a continuing impediment to understanding U.S. mortality rates." They suggested that "factors other than reuse germicides and reprocessing techniques are influencing mortality rates" and that center effects, confoundings with differential delivery of dialysis, or effects related to particular ownership status of dialysis units might explain the results.

In 1996 Feldman *et al.*, in a nonconcurrent cohort study of 27,938 ESRD patients who began renal replacement therapy with hemodialysis in 1986 and 1987 (a period before the widespread use of high-flux dialyzers), found that patients treated in free-standing dialysis units that disinfected dialyzers with peracetic acid mixtures had higher mortality than patients treated in dialysis units that did not reuse dialyzers (relative risk 1.10, $P = 0.02$) (29). They could not show a difference in survival between patients treated in units that used formaldehyde or glutaraldehyde and patient survival in free-standing units that did not reuse dialyzers, or between patients in hospital-based units that reprocessed dialyzers and those that did not. This was unit-level data, and the study suffered from the design flaw that patient-level data regarding reuse or comorbidity were not available. Small, well controlled, recent short-term clinical studies have not been able to establish differential risks of reuse (30).

In this issue of the Journal, Collins and colleagues, in a large study of the U.S. ESRD hemodialysis program using patient- and unit-specific data from the Health Care Financing Administration and the Centers for Disease Control and Prevention, and unitwide-based data on reuse techniques, report differential survival of patients treated in different types of dialysis facilities with different sterilants during different time periods, controlling for patient comorbidity (31). Multiple investigative strategies were followed. For instance, patients treated between 1991 and 1993 in free-standing units where reuse was employed had lower mortality risk compared with patients treated in nonprofit dialysis units that did not reuse dialyzers. Patients in free-standing units where formaldehyde and peracetic acid were the sterilants had lower mortality risk, but the authors were unable to demonstrate statistically significant differences in mortality risk for the smaller group of patients whose dialyzers were sterilized with glutaraldehyde. Likewise, there were no statistically significant differences in mortality risk for the smaller group of patients whose dialyzers were reused with any sterilant in hospital-based units. Free-standing, for-profit units had higher mortality risk than hospital-based units. Peracetic acid reuse in all units was associated with higher mortality risk during the period from 1989 to 1990, but not from 1991 to 1993. In a final analysis including 40 observations regarding relative mortality risks in subsets of patients treated with different reuse techniques in different dialysis settings with different profit status during different time periods, only five settings exhibited significantly higher or lower risks compared with those of the gold standard, nonprofit, hospital-based units not reusing dialyzers. However, the variability of the direction of the risks demonstrated in different dialysis unit types using disparate reuse techniques makes the use of Occam's parsimonious razor likely to result in self-inflicted nicks of the nephrologist's skin.

This is a large and important study that grows logically out of the previous literature, but it demonstrates the pitfalls associated with studies using huge fiscally based databases. The authors conclude "the association of reuse practices with mortality vary dramatically with different dialysis unit settings." This is undeniable, but the lessons to be learned from this observation are unclear. As the authors indicate, "the diverse dialysis unit and patient characteristics in the United States pose significant challenges to any national study on reuse safety and efficacy. . . " In addition, one of their conclusions is that the "findings suggest factors other than patient characteristics and reuse germicides can influence patient mortality." The results (and pitfalls) of such analyses depend on the analytic control techniques. For instance, to replicate previous investigations the authors attempted to limit the study population to patients treated with "conventional" dialysis. Therefore, units with more than 25% of patients treated with high-efficiency and high-flux dialyzers were excluded from the study. This decision removes from consideration a high proportion of contemporary patients in whom reuse is likely to be nearly universal. It is also virtually certain that in "reuse units," a certain proportion of patients refuse reprocessed dialyzers. Although this proportion has been reported as no greater than approximately 10% (29), if these patients for whatever reason are at different mortality risk, they could potentially confound the results. Furthermore, incident patients were not analyzed separately in this study. Combining incident and prevalent patients, as the authors note, may tend to allow a survivor advantage to be present in the prevalent patients considered at the outset of each study period. It would have been useful to examine outcomes in a large population limited to incident patients. Finally, in the present study, complex analyses use

interaction techniques that mix unit-level and patient-level data. Are these results interpretable? Are there possibilities that in such a large study, the levels of certainty achieved do not ensure that the findings are not a result of chance, or a consequence of the imprecision in the way the analytic questions have been asked, using the data available? In Table 7, *P* values might have helped the reader assess the strength of the relationships in the different cells with different numbers of subjects.

Alternatively, dialysis unit characteristics may be quite important—in fact, may be more important than the type of reprocessing techniques used—representing a true "center effect." A center effect, however, may not be due to a difference in reuse techniques and germicides *per se*, but rather may be due to other policies of large dialysis corporations, the dialyzers and unique hemodialysis techniques they employ, individual physicians' practices, or other unknown variables, merely reflected by specific reuse patterns. This quandary was pointed out nicely by Held *et al.*: ". . . the control group is not precisely the same in all respects as the treatment group. . . . Non reuse dialysis units may not be precisely the same as the reuse units even after controlling for measured characteristics" (27). After reading all of these studies, we are left wondering, is there an effect? And if so, what is the cause?

How reuse might cause differential mortality is open to question. Possibilities include effects on albumin balance in patients (32), sterilant toxic effects, effects on dialyzer clearance, or immune effects concomitant with a plethora of variables associated with different treatment and reuse techniques. The effect of type of ownership and setting of dialysis units on outcomes which may be mediated by particular reuse practices seems to be much more difficult to elucidate.

These issues and the differences between the findings in the different studies cited illustrate the problems inherent in large, observational studies that use databases designed primarily to track finances, that occasionally combine this information with patient-level data, and that often make global inferences about individual patient characteristics from unit-level data. Among such problems are selection bias; problems using codes (which may be designed to maximize financial outcomes) as precise diagnostic tools; and trends in dialytic techniques and the treatment of renal and comorbid diseases that may vary across time, geography, and units. It comes down to the basic issues of the presence of confounders, and association *versus* causality. Among all of the trends of the past two decades that may affect patient mortality, if the issues raised by reuse are salient, it is critical to distinguish causative, fundamental, and quantitatively important effects from those associated with other changes in dialytic treatment over time, which may be relatively quantitatively insignificant, or intertwined with confounders or covariates. To resolve these questions, prospective studies that collect data on the possible mediators of differential outcome thought to be related to reuse techniques should go far in determining whether there is indeed a tempest in the dialytic teapot. If the renal community deems that in fact there may be an association of reuse patterns with differential outcomes, randomized controlled trials are necessary to diminish confounding factors and bias.

Who will pay for such a trial or trials? The purveyors of the service would have an interest in determining the salutary or morbid consequences of a particular treatment to ensure the health of their patients. These studies must use methods that quantify, control, and distribute risk factors (*e.g.*, patient comorbidity, delivered dose of dialysis, and nutritional parameters) equally across the study population, using similar dialyzer types and including incident and prevalent populations. Such studies, rather than reviews of old data, are needed in the era of common use of synthetic dialyzers. The companies making specific germicides must not support the research in order to assure the renal community that the results are unbiased.

References

1. Shaldon S: Twenty-two years' experience with reuse. *Dial Transplant* 11: 569–570, 1982
2. Shaldon S: Dialyzer reuse: A practice that should be abandoned. *Semin Dial* 6: 11–12, 1993
3. Shaldon S: Reuse of dialyzers. *Nephrol Dial Transplant* 9: 1226–1227, 1994
4. Shaldon SH, Silva H, Rosen SM: The technique of refrigerated coil preservation hemodialysis with femoral venous catheterization. *Br Med J* 2: 672–674, 1964
5. Kant KS, Pollack VE, Cathey M, Goetz D, Berlin R: Multiple use of dialyzers: Safety and efficacy. *Kidney Int* 19: 728–738, 1981
6. Pollak VE, Kant S, Parnell SL, Levin NW: Repeated use of dialyzers is safe: Long-term observations on morbidity and mortality in patients with end-stage renal disease. *Nephron* 42: 217–223, 1986
7. Wing AJ, Brunner F, Brynger H: Mortality and morbidity of reusing dialyzers. *Br Med J* 2: 853–855, 1978
8. Cheung AK, Dalpias D, Emmerson R, Leypoldt JK: A prospective study on intradialytic symptoms associated with reuse of hemodialysers. *Am J Nephrol* 11: 397–401, 1991
9. Orringer EP, Mattern WD: Formaldehyde-induced hemolysis during chronic hemodialysis. *N Engl J Med* 294: 1416–1420, 1976
10. Kaehny WD, Miller GE, White WL: Relationship between dialyzer reuse and the presence of anti-N-like antibodies in chronic hemodialysis patients. *Kidney Int* 12: 59–65, 1977
11. Lewis KJ, Dewar PJ, Ward MK, Kerr DNS: Formation of anti-N-like antibodies in dialysis patients: Effect of different methods of dialyzer rinsing to remove formaldehyde. *Clin Nephrol* 15: 39–43, 1981
12. Hakim RM, Breillatt J, Lazarus JM, Port FK: Complement activation and hypersensitivity reactions to dialysis membranes. *N Engl J Med* 311: 878–882, 1984
13. Held PJ, Pauly M, Diamond L: Survival analysis of patients undergoing dialysis. *JAMA* 257: 645–650, 1987
14. Chenoweth DE, Cheung AK, Henderson LW: Anaphylotoxin formation during hemodialysis: Effects of different dialyzer membranes. *Kidney Int* 24: 764–769, 1983
15. Hakim RM, Lowrie EG: Effect of dialyzer reuse on leukopenia, hypoxemia and total hemolytic complement system. *ASAIO Trans* 26: 159–164, 1980
16. Kant KS, Pollack VE, Cathey M, Goetz D, Berlin R: Multiple use of dialyzers: Safety and efficacy. *Kidney Int* 19: 728–738, 1981

17. Shusterman NH, Feldman HI, Wasserstein A, Strom BL: Reprocessing of dialyzers: A critical appraisal. *Am J Kidney Dis* 14: 81–91, 1989
18. Agodoa L, Wolfe R, Port F: Reuse of dialyzers and clinical outcomes: Facts or fiction? *Am J Kidney Dis* 1998, in press
19. Cotter D, Thamer M, Sadler J, Kimmel PL: Secular trends in recombinant erythropoietin therapy among the U.S. hemodialysis population: 1990–1996. *Kidney Int* 1998, in press
20. U.S. Renal Data System: USRDS 1997 Annual Data Report. National Institutes of Health, National Institutes of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, April 1997
21. Hakim RM, Held PJ, Stannard DC, Wolfe RA, Port FK, Daugirdas JT, Agodoa L: Effect of the dialysis membrane on mortality of chronic hemodialysis patients. *Kidney Int* 50: 566–570, 1996
22. Kimmel PL: Psychosocial factors, behavioral compliance and survival in urban hemodialysis patients. *Kidney Int* 54: 245–254, 1998
23. von Albertini B, Bosch JP: Short hemodialysis. *Am J Nephrol* 11: 169–173, 1991
24. Ronco C: Hemofiltration and hemodiafiltration. In: *Hemodialysis: High Efficiency Treatments. Contemporary Issues in Nephrology*, Vol. 27, edited by Bosch JP, Stein JH, Churchill Livingstone, 1993, pp 119–133
25. Held PJ, Pauly M, Diamond L: Survival analysis of patients undergoing dialysis. *JAMA* 257: 645–650, 1987
26. National Institute of Diabetes and Digestive and Kidney Diseases: The USRDS Case Mix Study: Preliminary results on dialyzer reuse. Presented to an open meeting of the Food and Drug Administration, October 8, 1992
27. Held JP, Wolfe RA, Gaylin DS, Port FK, Levin NW, Turenne MN: Analysis of the association of dialyzer reuse practices and patient outcomes. *Am J Kidney Dis* 23: 692–708, 1994
28. Luehmann DA, Cosentino LC: Safety of dialyzer reuse with Renalin®: The untold story. *Dial Transplant* 23: 248–258, 1994
29. Feldman HI, Kinosian M, Bilker WB, Simmons C, Holmes JH, Pauly MV, Escarce JJ: Effect of dialyzer reuse on survival of patients treated with hemodialysis. *JAMA* 276: 620–625, 1996
30. Pereira BJG, Natov SN, Sundaram S, Schmid CH, King AJ: Impact of single use versus reuse of cellulose dialyzers on clinical parameters and indices of biocompatibility. *J Am Soc Nephrol* 7: 861–870, 1996
31. Collins AJ, Ma JZ, Constantini E, Everson S: Dialysis unit and patient characteristics associated with reuse practices and mortality: 1989–1993. *J Am Soc Nephrol* 9: 2108–2117, 1998
32. Kaplan AA, Halley SE, Lapkin RA, Graeber CW: Dialysate protein losses with bleach reprocessed polysulfone dialyzers. *Kidney Int* 47: 573–578, 1995