SEMINARS IN
NEPHROLOGY

Dialysis Outcomes as a Measure of Adequacy of Dialysis

Michael Butman and Allen R. Nissenson

Truly adequate dialysis would restore patients to full health, with functional status and length of life indistinguishable from others of the same age, sex, and race without chronic kidney disease. We are far from achieving such outcomes, however, in part because of the dearth of available evidence on which areas of care should be emphasized to get the greatest clinical and psychosocial benefits at the most affordable costs. A clear understanding of the strengths and limitations of currently available evidence can help guide researchers and clinicians in this field, and likely will lead to increasing emphasis on identification and management of comorbid conditions and a focus on preventative medicine. Optimal dialysis will be accomplished only when normal kidney functions are mimicked by artificial devices to a much greater extent than is currently the case.
Semin Nephrol 25:70-75

Hemodialysis therapy has been one of the true success stories in the annals of medical science. Before the availability of this treatment, the diagnosis of kidney failure was a death sentence. Overnight, however, with the availability of chronic dialysis, countless numbers of patients have lived with end-stage renal disease (ESRD), many experiencing an excellent quality of life. The number of patients with ESRD continues to grow, with recent estimates suggesting that more than 600,000 patients will be requiring dialysis by 2010.[1] In addition, recent studies have shown that nearly 20 million Americans likely have chronic kidney disease, most of whom will die from cardiovascular or other causes before they reach ESRD.[2] Although it is generally accepted that survival and quality of life of patients receiving a kidney transplant surpass that seen with dialysis,[3] the lack of available donor organs has resulted in only a small fraction of ESRD patients receiving this form of renal replacement therapy (RRT).

The technical ability to provide life-saving therapy to ESRD patients combined with the increasing number of patients who require RRT has been accompanied by enormous economic burdens on the health care system. In 1999 the total cost of the ESRD program in the United States was more than 17 billion dollars, and by 2010 it is estimated to be more than 28 billion dollars, raising concerns over the future viability and structure of the program.[4,5]

By the late 1980s it became clear to the nephrology community that patient outcomes were suboptimal. In 1989, at the Dallas symposium on the morbidity and mortality of dialysis patients, it was reported that the United States had the highest gross mortality rates when compared with other industrialized nations.[6] Nearly a quarter of dialysis patients die each year, with estimated survival after diagnosis of ESRD worse than that for breast and colon cancer. Five-year survival for new ESRD patients beginning dialysis from 1982 to 1987 in the United States, Europe, and Japan was analyzed by Held et al[7] and reported in 1987. US patients were older and were more likely to have diabetes than were patients from Europe or Japan, and survival analyses were performed after adjustment for these differences. Japan had the highest rate of survival, followed by Europe and the United States, with 5-year survival rates of 54%, 48%, and 40%, respectively. As patient age increased, the differences were least for patients with diabetes and greatest for nondiabetic patients. US death rates were twice as high during the first 90 days of dialysis as well.[7]

The dissemination of these findings drew the attention of patients, physicians, and health care agencies alike. Through their concerted efforts there was increased research focused on understanding the variables associated with improved ESRD patient outcomes. Over the past decade, guidelines were developed by the Renal Physicians Association and the National Kidney Foundation targeting specific dialysis-re-

From the Division of Nephrology, Department of Medicine, David Geffen School of Medicine at UCLA.
Supported in part by National Institutes of Health training grant T32-DK07789, and by the Richard Rosenthal Dialysis Fund (A.R.N.).
Address reprint requests to Allen R. Nissenson, MD, UCLA Medical Center, 200 Medical Plaza, Suite 565, Los Angeles, CA 90095. E-mail: anissenson@mednet.ucla.edu

0270-9295/05/$-see front matter
doi:10.1016/j.semnephrol.2004.09.011

lated domains in the care of dialysis patients. Recent analyses have documented the role of these efforts in somewhat improving ESRD patient outcomes, however, there are still unacceptably high rates of mortality and morbidity, poor patient quality of life and satisfaction, and high costs for this patient population.[1,8-11]

This issue of *Seminars in Nephrology* focuses on adequacy of dialysis and several potential determinants of this. Adequate dialysis is the amount of treatment that achieves certain biochemical targets and patient well-being.[13] As pointed out by Twardowski,[12] however, what is desired is optimal dialysis, something to this day that seems even more difficult to achieve. Assessing adequacy of dialysis, and prioritizing the key factors impacting on adequacy, requires an understanding of some basic aspects of the use of evidence-based medicine because the available data in this field are sparse and not always of the highest quality. The clinical basis of quality assessment is found in evidence-based medicine, whereas the methodology for measurement and the design of interventions is based on statistical process control and continuous quality-improvement theory.

Measurement Frameworks for Assessing Quality of Care

To develop valid, actionable guidelines of care for patients with ESRD, it is helpful to have a framework for assessing the quality of medical care. Such a framework has been proposed in the seminal work related to health care quality by Donabedian.[13] In this model, Donabedian[13] proposes 3 categories of quality measures: structure (S), process (P), and outcome (O). Structure is defined as the stable elements that form the basis of the health care system being evaluated. For example, in the ESRD program, structure would include the organizational and physical aspects of dialysis care such as mix and qualifications of professional staff, re-use of dialyzer membranes, or for-profit status of the dialysis unit. Process, on the other hand, is defined as the people, procedures, and equipment present within the system that interact to produce a given outcome (ie, what is performed within the structure). For ESRD, this would be those components or activities, technical or interpersonal, necessary to provide dialysis treatment reflected by such markers as delivered dose of dialysis or achieved hemoglobin level. Finally, outcome is defined as the desired states resulting from care processes (ie, what happens to the health of the patient as a consequence of medical practices and interventions).[14] There are 2 types of measures within the broad domain of outcomes measures: technical and interpersonal.[15] Technical outcomes measures refer to those measures encompassing the physical and functional aspects of care such as mortality or hospitalization, whereas interpersonal outcomes measures refer to measures that are more subjective such as patient satisfaction or the influence of care on the patient's quality of life as perceived by the patient.[15]

In addition to providing a framework for assessing quality of medical care, use of the S-P-O paradigm also serves to identify areas that may be targeted for quality improvement efforts. The quality improvement efforts in the ESRD program initially focused on the structural and procedural components of the framework of ESRD care.[14] Work in these areas suggested that structural factors have a significant impact on patient outcomes.[16] For example, there have been studies examining the structural factor of profit status of dialysis facilities and the quality of care delivered.[9,17-19] Initially, it was found that there was a correlation between a facilities' profit status and the rates of mortality (nonprofit facilities had lower mortality rates). Although this finding had been challenged, recent data suggest that this may in fact be accurate, despite the ability of for-profit facilities to achieve better performance on intermediate outcomes such as hitting the dose of dialysis target (Owen, William, personal communication, June 2004).

Other studies examining different aspects of processes of care, such as the frequency and type of physician-patient interaction, showed improvement in process-related outcomes, including patient satisfaction with the physician component of care, when the number of interactions with physicians was greatest. There was no effect of such interactions on mortality, however. In fact, there are data to suggest that it is the extent to which physicians participate in multidisciplinary rounds, as opposed to the time spent at the bedside, which results in a greater impact on morbidity and mortality.[20] Other process indicators, such as those included in the Centers for Medicare and Medicaid Services (CMS) clinical performance measures (CPMs) dataset (ie, dose of dialysis, hemoglobin level) also only weakly correlate with patient survival.[11]

Outcomes Research

Whether process measures of care are more valid and precise measures of quality than are outcome measures remains unresolved.[21] Nonetheless, the use of evidence-based medicine, primarily through the use of clinical practice guidelines, performance measures, and continuous quality improvement approaches has enabled patients, providers, and purchasers to make more rational decisions when faced with health care choices, even if the impact on outcomes (mortality, hospitalization) has been disappointing. Outcomes research addresses medical effectiveness (ie, how well prevailing treatments work in different clinical practice settings). The outcome measured may be intermediate (eg, percent of patients with functional fistulae or amputation or saved vision) or final (eg, mortality rates, hospitalization rates, patient functional status). Furthermore, in patients on RRT, outcomes often are confounded by many variables related to structure or process, such as patient preference, comorbidities, and system factors (ie, dialysis center procedures, or involvement of multiple health care providers). The information obtained from outcomes research allows the allocation of resources in those areas and for those interventions that are most likely to benefit the patient.

Clinical Performance Measures

A good outcome, however, does not necessarily equate with ideal patient care. Furthermore, a good outcome or a bad outcome may be related to factors other than what was performed by the clinician. For example, comorbidity and poverty may not be related to the intervention performed by the clinician, however, they may both strongly affect the outcome (morbidity and mortality) measured.[22] CPMs attempt to address the confounding factors by linking the outcome with the intervention. By doing so, the impact of the intervention on the outcome measured can be appreciated fully and, ultimately, the quality of medical care provided can be improved. CPMs are designed to evaluate the process or outcomes of care associated with the delivery of clinical care. The outcome measure is the result of this performance.

The development and use of CPMs has been integral in the development of guidelines for improving ESRD patient care.[23,24] In 1998, the Balanced Budget Act required CMS to develop and implement a method to measure and report the quality of renal dialysis services provided under the Medicare program by January 2000. To implement this legislation, CMS funded the development of CPMs based on the National Kidney Foundation's Dialysis Outcome Quality Initiative (DOQI) Clinical Practice Guidelines.[23,24]

Phase I (April 1998–January 1999) involved the prioritization of the DOQI Guidelines as to their feasibility of being converted into CPMs, the development of algorithms for the applications of the CPMs, and the development of proposed data collection instruments, data specifications, and methodology for the collection of the CPMs. Four work groups, composed of representatives from the renal community and CMS, were established to assist a contracted entity (PRO-West) in these activities.[23,24]

Sixteen ESRD CPMs (5 for hemodialysis adequacy, 3 for peritoneal dialysis adequacy, 4 for anemia management, and 4 for vascular access) were developed and delivered to CMS in December 1998. Phase II of the project (February 1999–March 2000) involved the pilot testing of the CPMs (testing for reliability and validity). Under the direction of CMS, PRO-West conducted the pilot testing of the CPMs. The pilot testing methodology was the same as that used for the ESRD core indicators project (a random national sample of adult hemodialysis patients, stratified by network area, and a random national sample of adult peritoneal dialysis patients) and was completed in 1999.[23,24]

That same year, the ESRD core indicators project was merged with the ESRD CPMs project and the project is now known by the latter name. The ESRD CPMs are similar to the core indicators with the addition of measures for vascular access. The ESRD CPMs are collected annually on a national random sample of adult hemodialysis and peritoneal dialysis patients.[25]

Although these dialysis-focused measures are used to measure performance, and performance has improved in these areas, primary outcomes (mortality and morbidity) have remained static, consistent with the work of Lowrie et al,[11] who showed that only 15% of the variability in dialysis patient mortality could be accounted for by these measures.[23,24] It is likely, therefore, that other aspects of care, particularly those focused on associated comorbid medical conditions, are key in determining patient outcomes, as discussed later.[26]

Quality Measurement Based on CPMs and Outcomes

By using the aforementioned CPMs, dialysis facilities, working closely with nephrologists, have done an excellent job of improving intermediate outcomes in dialysis patients. The delivered dose of dialysis has increased steadily on average, and the fraction of patients achieving the minimum standard of dialysis dose recommended by the National Kidney Foundation DOQI now exceeds 89%.[25,27] Similarly, the fraction of patients achieving the minimum hemoglobin level currently recommended also has increased steadily to its current level of 76%.[25]

Although there is clear evidence that low delivered doses of dialysis and low hemoglobin levels are associated with increased mortality and morbidity, achieving the minimum recommended targets in these areas has not had an impact on overall morbidity and mortality in this patient population. Data from the US Renal Data System (USRDS) clearly show that mortality in dialysis patients has not improved significantly over the past decade, despite the improvements in dialysis-related performance.[1] The most recent USRDS report states that, "adjusted first-year death rates have not improved since 1994 in either incident or prevalent populations." Although some may say that a stable mortality in the face of a population of increasing complexity is in fact an improvement, there is no scientific evidence to support this contention. Similarly, hospital days for dialysis patients continue to exceed 15 per patient per year, with no sign of improvement. The USRDS states that, "In the past five years, hospital days per admission have remained constant for the hemodialysis patients...differences in age, gender, race, and diabetic status do not explain the stability of hospitalization rates in ESRD patients over the last 10 years."[1]

Limitations of Outcomes Research

The inability to impact outcomes significantly may in part be related to the type and strength of evidence that has led to an emphasis on dialysis-related outcomes to improve quality. When considering this issue it is useful to understand the strengths and limitations of the study designs that are used to generate conclusions regarding the care of ESRD patients because it is the results of published studies that are used to develop the clinical practice guidelines that currently are emphasized. An excellent review of this topic has been published recently in a series of articles by Szczech et al.[28] A few of the key points are worth reemphasizing.

The most common study designs used in published studies on outcomes in ESRD patients include randomized controlled, cohort, and case control. Case control is the most

common study design in the ESRD literature. In such studies, patients are selected for inclusion based on the presence or absence of a particular end point. Patients reaching that outcome are referred to as *cases,* whereas patients who have not reached that outcome are referred to as *controls*. The frequencies of potential risk factors are compared among cases and controls. The rigor of such studies depends on whether there is a standardized definition for both cases and controls. In the absence of a standard definition, any similarity or difference among cases may be related to features of the disease or variations in the definition of disease, rather than the outcome of interest. The lack of a standardized definition challenges the internal and external validity of the conclusions. Additionally, methods for case selection should allow all cases from a subpopulation to be at equal probability of being selected. If a subgroup or certain cases have a greater probability of being selected than others, the assessment of risk factors will be skewed toward the group that is different from the entire population.[28]

The relationship of cases to time of disease onset also should be examined. The inclusion of patients who are prevalent to the disease process may result in a bias through the selection of whatever factors allowed them to survive to that point. With respect to the ESRD population, patients with greater survival are more likely to be black, have better nutritional stores, and are less likely to have diabetes. Case-control studies involving ESRD patients need to be designed to allow for the effect, if any, of prevalent and incident status on the assessment of risk factors and outcomes.[28]

The method of selection of controls is of equal importance in case-control studies. Controls should reflect the general population of individuals from which the disease or outcome is possible to develop. Unfortunately, there is often no ideal control group. In these situations, multiple control groups may be selected, however, one can never completely control the differences between groups. This is apparent in the early data comparing the survival among patients receiving kidney transplants with dialysis patients who did not receive a transplant. The survival benefit associated with living related transplantation may have been confounded by the fact that the transplant recipients were younger and less likely to have diabetes than the dialysis patients.[28]

In contrast to case-control studies, cohort studies are characterized by the recruitment of participants based on exposure, with subsequent observation for the development of a disease end point. At the time of enrollment, exposure status has been defined and patients are free of the disease or outcome under investigation. The study may be performed either retrospectively or prospectively.[28]

Although different from case-control studies, cohort studies have their own limitations and it is important that the reader be aware of them. First, the methods used to identify patients and ensure complete capture of all patients who have been exposed, or at least a representative sample of that group, must be designed carefully. The complete capture of all exposed patients in a random or unbiased manner provides the most accurate estimation of the strength of association between exposure and outcome. Second, in selecting the study population, the primary requirement for validity is the ability to obtain complete and accurate information on all participants with respect to exposure and outcomes. The sources of data, exposure information, and outcome data need to be similar for all patients. If methods suggest a differential effort or manner was undertaken among patients, selection bias in ascertaining the strength and direction of an association may be introduced. Furthermore, sources of indication bias in cohort studies may occur in those studies in which the exposure is an administered treatment and in which the choice of therapy or the choice to provide therapy may be influenced by disease factors that impact outcome. If the indication for treatment affects the outcome of interest, the association between treatment and outcome may be altered by the reasons for which treatment was offered.[28]

A review of a retrospective study by Ma et al[29] shows some of the aforementioned limitations of cohort studies. Ma et al[29] examined the question of whether the hematocrit level itself or other factors related to achieving a given hematocrit level were associated with a decrease in mortality rate. By using all prevalent Medicare hemodialysis patients surviving over a 6-month period, hematocrit levels were compared between patients whose hematocrit levels ranged between 30% and 33% and those whose hematocrit levels ranged between 27% and 30%. It was found that the latter had a higher mortality at 1 year than the former. Although the method for patient identification provided a sample of the majority of patients receiving dialysis in the United States, if one examines the source of the data, the following limitations are revealed. First, entry into the cohort required that the patients be Medicare beneficiaries. Second, the included patients' hematocrit values were obtained from billing data, which was linked to epoetin reimbursement. As a result, patients whose hematocrit levels were greater than 36%, who were not receiving epoetin, or did not have available hematocrit data, were excluded from the analysis. Although internal validity is not affected with the approach taken, the generalizability of the conclusions regarding patients receiving hemodialysis who do not require epoetin is affected, and no conclusions about this group of patients can be derived from this study.[28]

Unlike the limitations associated with bias encountered in the aforementioned study designs, with randomized trials, indication bias or the potential for bias in treatment allocation to study groups is removed. If randomization is successful, it subsequently will isolate the effect of the intervention and any difference in outcomes may be attributed entirely to the treatment course. A cause-and-effect relationship subsequently may be established. Nonetheless, the selection of a study population remains important to ensure generalizability to the entire patient population. Some factors involved in selecting a study population that may affect the generalizability are still unavoidable. They include those factors that increase the likelihood that an individual will agree to participate and remain within a study. They may include age, sex, socioeconomic status, and education. To the extent that these factors affect subsequent morbidity and mortality, their effect should be considered when examining the study population as a whole.

A frequently cited study by Besarab et al[30] shows that even randomized study designs can be problematic. In their study, hemodialysis patients with heart failure or ischemic heart disease were randomized to receive a dose of epoetin to achieve and maintain a hematocrit of 42% ± 3% or 30% ± 3%. The primary end points were all-cause death and/or first nonfatal myocardial infarction. Randomization resulted in matched groups of patients. The study was stopped early when it was determined that it was statistically impossible for the group with the higher hematocrit level to have an event-free advantage over the group with the lower hematocrit level, thus negating the hypothesis that drove the study. The difference in outcomes between the groups, however, was not statistically significant, and within each group the higher the hematocrit level, the better the outcome. The common interpretation of this study, however, is that it is not safe for dialysis patients with heart disease to have a normal hematocrit level. The correct interpretation is that this study did not show a survival benefit of a normal hematocrit level in patients *randomized* to a normal hematocrit level.[28,30]

Conclusion

Adequacy of dialysis is best viewed in its broadest terms—this form of RRT will prove to be adequate only when the survival and quality of life of dialysis patients equals or exceeds that of similar individuals without kidney disease. To help us achieve this lofty goal, and to enable us to measure our progress along the way, it is necessary to have a common framework with which to assess the quality of care delivered to dialysis patients, such as that of Donabedian,[13] always keeping in mind the key outcomes of mortality, morbidity (usually hospitalization), quality of life, and patient satisfaction. Investigators and readers of the literature must be knowledgeable regarding outcomes research, its strengths and limitations, and the purpose and use of practice guidelines and clinical performance measures to drive improvements in care. Furthermore, the reader should be familiar with the differences between clinical study designs and their limitations because the conclusions from these studies serve as the basis for guideline development, regulatory oversight, and standards of practice. The articles in this issue of *Seminars in Nephrology* take an in-depth look at selected measures of care related to the delivery of dialysis and their impact on dialysis patient outcomes. It must be kept in mind, however, that achieving accepted performance on these measures is necessary, but not sufficient in ensuring adequate dialysis in the broader sense. Additional attention needs to be placed on identification and management of medical comorbid conditions including cardiovascular disease, diabetes, and hypertension, as well as on preventative medicine, particularly immunizations (influenza, pneumonia). Outcomes improve when such an approach is taken.[26,31-32] For example, influenza vaccination in hemodialysis patients was associated with a 16% decrease in the risk for hospitalization for pneumonia and a 36% decrease in the risk for death from infection.[33] Finally, to achieve adequate dialysis there must be significant technical advances in the delivery of RRT, with the goal to emulate the function of normal kidneys.[34]

References

1. U.S. Renal Data System: 2003 Annual Data Report. Atlas of End-Stage Renal Disease in the United States. Bethesda, MD, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2003
2. National Kidney Foundation: K/DOQI clinical practice guidelines for chronic kidney disease: Evaluation, classification and stratification. Am J Kidney Dis 39:S1-S266, 2002 (suppl 1)
3. Meier-Driesche H, Ojo AO, Port FK, et al: Survival improvement among patients with end-stage renal disease: Trends over time for transplant recipients and wait-listed patients. J Am Soc Nephrol 12: 1293-1296, 2001
4. Nissenson AR: Restructuring the ESRD payment system in the United States. Kidney Int 66:466-476, 2004
5. Nissenson AR, Rettig RA: Medicare's end-stage renal disease program: Current status and future prospects. Health Aff (Millwood) 18:161-179, 1999
6. Hull A, Parker T: Proceedings from the Morbidity, Mortality, and Prescription of Dialysis Symposium, Dallas, Texas, September 15 to 17, 1989. Am J Kidney Dis 15:375-383, 1990
7. Held PJ, Brunner F, Odaka M, et al: Five year survival for end stage renal disease patients in the United States, Europe, and Japan, 1982-1987. Am J Kidney Dis 15:451-457, 1990
8. Medicare Payment Advisory Commission: Report to Congress: Modernizing the outpatient dialysis payment system. Published by MedPAC, Washington DC 2003
9. McClellan WM, Soucie JM, Flanders WD: Mortality in end-stage renal disease is associated with facility-to-facility differences in adequacy of hemodialysis. J Am Soc Nephrol 9:1940-1947, 1998
10. Collins AJ, Roberts TL, St. Peter W, et al: United States Renal Data System assessment of the impact of the National Kidney Foundation-Dialysis Outcomes Quality Initiative guidelines. Am J Kidney Dis 39: 784-795, 2002
11. Lowrie EG, Teng M, Lacson L, et al: Association between prevalent care process measures and facility specific mortality rates. Kidney Int 60: 1917-1929, 2001
12. Twardowski ZJ: PET—a simpler approach for determining prescriptions for adequate dialysis. Adv Perit Dial 6:186-191, 1990
13. Donabedian A: Evaluating the quality of medical care. Milbank Q 44: 166-203, 1966
14. McClellan WM, Goldman RS: Continuous quality improvement in dialysis units: Basic tools. Adv Ren Replace Ther 8:95-103, 2001
15. Donabedian A: Quality assessment and assurance: Unity of purpose. Diversity of means. Inquiry 25:173-192, 1988
16. Hammermeister KE, Shroyer AL, Sethi GK, et al: Why it is important to demonstrate linkages between outcomes of care and processes and structures of care. Med Care 33:OS5-OS16, 1995
17. Devereaux PJ, Schunemann HJ, Ravindran N, et al: Comparison of mortality between private for profit and private not for profit hemodialysis centers: A systematic review and meta-analysis. JAMA 288:2449-2457, 2002
18. Garg PP, Frick KD, Diener-West M, et al: Effect of the ownership of dialysis facilities on patient's survival and referral for transplantation. N Engl J Med 341:1653-1660, 1999.
19. Held PJ, McCullough KP, Gillespie BW: survival among patients in for profit and not for profit hemodialysis facilities. J Am Soc Nephrol 2002 (abstr)
20. Plantinga LC, Fink NE, Jaar BG, et al: Association of frequency of patient care rounds with mortality and intermediate clinical outcomes in hemodialysis patients. J Am Soc Nephrol 14:3, 2003 (abstr)
21. Rubin HR, Pronovost P, Diette GB: The advantages and disadvantages of process-based measures of health care quality. Int J Qual Health Care 13:469-474, 2001
22. Goldberg MJ: An Introduction to Outcomes and Performance Measures. Proceedings from the First Annual Are We Helping? How Do We

Know? National Symposium of the Boston Children's Institute of The Home for Little Wanderers, Boston, MA, May 11, 2000
23. McClellan WM, Frankfield DL, Frederick PR, et al: Improving the care of ESRD patients: A success story. Health Care Financing Review 24: 89-101, 2003
24. Frederick PR, Maxey NL, Clauser SB, et al: Developing dialysis facility-specific performance measures for public reporting. Health Care Finance Review 24:37-51, 2002
25. Centers for Medicare and Medicaid Services: 2002 Annual Report, End Stage Renal Disease Clinical Performance Measures Project. Baltimore, MD, Department of Health and Human Services, Centers for Medicare and Medicaid Services, Center for Beneficiary Choices, 2002
26. Nissenson AR: What common practices in dialysis units can be altered to improve patient care? Semin Dial 17:12, 2004
27. NKF-K/DOQI: Clinical Practice Guidelines for Hemodialysis Adequacy. New York, National Kidney Foundation, 2001
28. Szczech LA, Coladonato JA, Owen WF: Study designs and their potential influence on conclusions. Semin Dial 15:207-211, 2002
29. Ma JZ, Ebben J, Xia H, et al: Hematocrit level and associated mortality in hemodialysis patients. J Am Soc Nephrol 10:610-619, 1999
30. Besarab A, Bolton WK, Browne JK, et al: The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. N Engl J Med 339:584-590, 1998
31. National Kidney Foundation: K/DOQI clinical practice guidelines for managing dyslipidemias in chronic disease. Am J Kidney Dis 41:S1-S92, 2003
32. Flauto RP, Leon JP, Sehgal AR: The provision and outcomes of diabetic care in hemodialysis patients. Am J Kidney Dis 41:125-131, 2003
33. Gilbertson DT, Unruh M, McBean AM, et al: Influenza vaccine delivery and effectiveness in end-stage renal disease. Kidney Int 63:738-743, 2003
34. Nissenson AR, Pergamit G, Edelstein M, et al: The human nephron filter-1 (HNF-1): Toward a continuously functioning, implantable artificial nephron system by applying nanotechnology (NT) to renal replacement therapy (RRT). Am Soc Nephrol Annual Meeting, 2003. Available at: www.asn-online.org