What Has Outcomes Research Taught Us About Evidence-Based Treatment of End-Stage Renal Disease?

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The incidence and prevalence of end-stage renal disease (ESRD) has increased steadily over the past decade [1]. Additionally, the population beginning dialysis is older, with more comorbidities. In spite of these trends, first-year death rates in hemodialysis and peritoneal dialysis patients have decreased by 11% and 27%, respectively, between 1989 and 1998. While first-year mortality remains high at slightly more than 19%, these improvements are nonetheless striking [1]. In addition to advancements in the treatment of cardiovascular disease and other comorbidities frequently seen among ESRD patients, improvements in the processes of care specific to ESRD have likely contributed to improved survival.

Evidence-based medicine is the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients [2]. The United States Renal Data Service (USRDS) and other similar patient-oriented databases provide a unique tool for epidemiologic and outcomes researchers studying ESRD. Using these large datasets, which capture all U.S. dialysis patients and include large population-based samples, researchers in nephrology have been able to observe relationships, generate hypotheses regarding mechanism of effect, and translate the findings to the trial setting. While each database has its own advantages and disadvantages (eg, only Medicare-eligible patients are included in the USRDS database, which may [minimally] affect external generalizability), they provide valuable tools for understanding the effects of practice patterns on outcomes.

This review addresses 3 areas of care that have been associated with mortality risk for ESRD patients receiving hemodialysis: the optimal dose of dialysis, level of anemia correction, and management of malnutrition. Evidence from research in these 3 areas is examined to reveal how conclusions drawn from observational studies were later used to design and implement randomized trials aimed at further defining best care practices for ESRD patients.

Dialysis Dose

The quantifiable amount of dialysis delivered to a patient receiving hemodialysis can be measured using a number of different parameters, including the urea reduction ratio (URR) and $Kt/V$ (where $K$ = whole body urea clearance, $t$ = time on dialysis, and $V$ = volume of distribution for urea). While each may have its advantages and disadvantages in terms of ease of measurement or reproducibility, both have been associated with outcomes among dialysis patients. In general, as the dose of dialysis rises, the mortality risk for ESRD patients falls. Because URR is considered the preponderant measure of dialysis dose [3], outcomes associated with this measure of dialysis are presented here.

URR is based on the fractional reduction of blood urea nitrogen concentration (BUN) during a single hemodialysis treatment. URR is calculated by dividing the decrease in BUN (predialysis minus postdialysis BUN) by the predialysis BUN and is expressed as a percentage [4–6]. Several studies demonstrate an association between the amount of hemodialysis and mortality among ESRD patients [4,7–9] and a plateau for reduction of mortality risk at or around a URR of 60% to 65%, beyond which no further improvement in survival is seen [4,10]. Another study demonstrated that a URR of 70% to 74% was associated with an increased risk of death as compared with a URR of 65% to 69% [8]. This paradoxical increase in mortality risk among patients with greater doses of dialysis has been referred to as a J-shaped relationship. In multiple cohort analyses, decreasing albumin, decreasing creatinine, and decreasing body weight have all been repeatedly associated with increasing mortality [4,10–16]. Decreasing albumin, creatinine, and body weight are also markers of poorer nutritional status and are associated with increasing URR due to smaller volumes of distribution among patients in whom these parameters are depressed [17] (Figure 1). Another observational cohort study suggested that mortality risk continued to fall as URR rose above 65% [7].
The results of these observational studies differ, and they do not clearly define the “optimal” dose of dialysis. Based on these data, however, 3 national organizations, including the Health Care Financing Administration (HCFA), advocated for a URR of 65% as the threshold for “adequate” hemodialysis [3,5,6,18,19]. After establishing this as a benchmark of care in the mid 1990s, an increase in dialysis dose was seen. According to the 2001 National ESRD Core Indicators Report, a profile of patient-specific dialysis practices, the mean URR in U.S. hemodialysis patients increased from 62.7% in 1993 to 71.4% in 2000 [20]. In 2002, the effect of nutritional status as defined by body mass index (BMI) on the relationship between dialysis dose and mortality was confirmed [21]. This retrospective observational study used data from HCFA on patients who began hemodialysis between April 1997 and December 1998. The study demonstrated an association between decreasing BMI and increasing mortality. However, within tertiles of patients based on their BMI, the risk of death continued to decrease as URR increased over 65%. Also, for any given URR, the risk of death for individuals increased as BMI declined.

Recognizing the limitations of the studies based on observational data, the HEMO study was designed to test the effect of dialysis dose on morbidity and mortality among hemodialysis patients [22]. The study, begun in 1995, randomized patients to receive a dialysis dose corresponding to the established threshold for adequacy (URR of approximately 65%) or a higher dose (URR greater than 70%). While results are preliminary, there was no difference in mortality or hospitalization rates among groups in either treatment arm at 5 years. While subgroup analyses may suggest that groups based on gender and age may differ slightly in these results, this trial demonstrates that among all hemodialysis patients, there is no mortality benefit conferred by receiving a dialysis dose higher than the established benchmark.

**Anemia Correction**

Anemia in most patients receiving dialysis is due to reduced renal erythropoietin production and to a lesser extent decreased red cell survival, with iron deficiency also playing a role [23]. Treatment with agents such as epoetin alfa (Epogen, Amgen, Thousand Oaks, CA) generally results in increased hemoglobin or hematocrit and anemia correction. Observational datasets estimating the association between hemoglobin and mortality among dialysis patients demonstrate that higher hemoglobin is consistently associated with longer survival [24,25]. Among the cohort of patients receiving hemodialysis during 1993 through National Medical Care, one of the country’s largest dialysis providers, patients with hemoglobin levels of less than 8.0, 8.0 to 9.0, and 9.0 to 10.0 mg/dL all had a greater risk of mortality at 1 year (OR, 1.5, 1.3, and 1.25, respectively; all \( P = 0.0001 \)) as compared with patients with a hemoglobin of 10.0 to 11.0 mg/dL [24] (Figure 2). The mortality risk among patients with a hemoglobin greater than 11.0 mg/dL did not differ from that of the reference group.

Another retrospective cohort study examined Medicare hemodialysis patients surviving the period 1 July to 31 December 1993 [25]. As compared with patients whose hematocrit measurements ranged between 30% and 33%, patients with hematocrits of less than 27% and 27% to 30% had an increased risk of mortality at 1 year (OR, 1.51 and 1.20 [95% CI, 1.44–1.59 and 1.16–1.25], respectively). There was a decreased risk of mortality for patients with a hematocrit of 33% to 36% as compared with the reference group (OR, 0.90 [95% CI, 0.85–0.95]).

As observational data have limited ability to establish cause and effect, a multicenter randomized trial was designed to determine whether improved outcomes were truly related to better anemia correction rather than to the less easily defined factor of a patient’s ability to “achieve” a higher
hemoglobin or hematocrit. The randomized, prospective, open-label trial [26] studied hemodialysis patients with congestive heart failure or ischemic heart disease. Patients were randomized to receive doses of epoetin alfa sufficient to achieve and maintain a hematocrit of either 30% or 42%, and were followed for the development of all-cause death and first nonfatal myocardial infarction. The study was stopped early, with patients in the 2 treatment groups reaching the endpoint (the combination of death and myocardial infarction) at similar rates. Based on these results, there was no mortality benefit to being randomized to a treatment to achieve a higher hematocrit.

While this is another example of observational evidence being used to design a trial intended to more definitely establish benchmarks of care (ie, the appropriate target for anemia correction), because of the seemingly contradictory results between studies, a secondary analysis of the later trial should be considered. In the randomized trial, the primary analysis was performed using an intention-to-treat analysis. However, when patients were analyzed in an “as treated” manner, a survival benefit similar to that observed in the observational cohort studies [24,25] was observed. As hematocrit increased, the risk of mortality and nonfatal myocardial infarction decreased (RR, 0.7; P < 0.001, for each 10% increase in hematocrit) [26] (Figure 3). As these results are similar to those of the cohort studies, it could be hypothesized that a third factor associated with hematocrit may confer the mortality benefit. Individual patients may experience a relative “resistance” to epoetin based on the presence of infection or other causes of a systemic inflammatory state. Arguably, the degree to which a patient responds to epoetin may be related to the lack of this inflammatory state. It may subsequently be hypothesized that the lack of an inflammatory state and the patients’ “ability” to respond to epoetin may be related in part to the beneficial association seen in these studies.

Although the secondary analysis does not use the intention-to-treat design that normally would be used in the practice of evidence-based medicine, the results demonstrated are compelling and consistent with the prior cohort studies. The association between hematocrit and death was reexamined in a more contemporary dataset of Medicare-eligible patients [27]. This analysis suggested that there was no difference in death risk among patients with hematocrit values of 36% and greater as compared with patients with hematocrit values of 33% to 36%, but hospitalization rates were lower among patients with higher hematocrits. While this confirms the associations previously demonstrated, it is clear that further research to understand the effect of inflammation in these relationships is necessary. Using these and other studies, the 2000 clinical practice guidelines developed by the National Kidney Foundation as part of their Kidney Disease Outcomes Quality Initiative suggest a goal hematocrit of 33% to 36% among ESRD patients [28].

Malnutrition
While the observations regarding malnutrition and mortality are similar to those seen with dialysis dose and anemia, assessing the role of malnutrition and investigating ways to minimize its associated mortality risk among ESRD patients is considerably more complicated.

Whether malnutrition is defined based on commonly used laboratory-based surrogates of protein-calorie nutrition (eg, albumin, creatinine, and cholesterol) or conventional anthropometric measures, between 16% and 54% of ESRD patients can be categorized as malnourished [11,15,29–31]. Poor nutrition is a major risk factor for mortality and morbidity among
patients receiving maintenance hemodialysis [12–15, 32–36], and a statistical association between mortality and malnutrition among ESRD patients exists for each of the above-mentioned definitions [4,33,34].

The most striking of these associations is the one that exists between mortality and albumin. In a retrospective analysis of 13,473 patients receiving their dialysis care through National Medical Care from 1 October through 31 March 1990, Owen et al. [4] observed that serum albumin concentration was a more powerful (21 times greater) predictor of death than URR, as albumin fell, the relative risk of mortality rose. A serum albumin of 3.5 to 3.9 g/dL was associated with an odds ratio of death of 1.48 as compared with an albumin of 4.0 or greater. Mortality risk was even higher among patients with albumin of 3.0 to 3.4 g/dL (OR, 3.13). Alarmingly, 60% of the patients had serum albumin concentrations predictive of an increased risk of death (values below 4.0 g/dL).

Multiple etiologies may contribute to malnutrition in the ESRD patient, including decreased dialysis prescription, drug toxicity, and gastroparesis. It has been suggested that some of the laboratory surrogate markers for malnutrition in ESRD patients reflect additional disease processes, such as inflammation [37,38]. This is supported by evidence that hypoalbuminemia is inversely correlated with levels of commonly measured laboratory surrogates of inflammation, such as alpha-1-macroglobulin, ferritin, serum amyloid A, and C-reactive protein (CRP) [38,39]. This putative link between hypoalbuminemia and inflammation is especially provocative in the context of the association between elevated CRP levels and increasing mortality risk among ESRD patients [38]. These findings do not dismiss malnutrition as an etiology in increased death risk among dialysis patients but suggest a multifactorial pathobiology best characterized as a matrix that leads to mortality.

Therefore, while similar links have been established (ie, the association between markers of malnutrition and mortality), these markers have not been established as benchmarks of care. This is because after reversible causes of malnutrition (eg, gastroparesis and inadequate dialysis dose) have been ruled out, studies do not definitively establish that intervention—either through oral supplements or intradialytic parenteral nutrition—is able to affect malnutrition or the process (ie, inflammation) that may be contributing to it. While preliminary evidence suggests that oral essential amino acids may be modestly beneficial to biochemical markers of malnutrition among patients with significant hypoalbuminemia, further study of their effect on clinical outcomes is required [40]. Additionally, while a number of studies suggest that intradialytic parenteral nutrition may be beneficial, conclusions based on them are limited by biases introduced by their designs. In one study, intradialytic parenteral nutrition was associated with a 12% rise in plasma albumin concentration and an apparent improvement in survival (64% versus 52% in patients not receiving intradialytic parenteral nutrition) [41], but the study was retrospective and intradialytic parenteral nutrition was compared to no therapy rather than to other nutritional interventions.

The clinical assessment and treatment of malnutrition needs to be better understood. Because the pathobiology of malnutrition is likely closely related to an inflammatory state rather than merely to protein-calorie deficiency, stronger evidence is necessary to link the potential for improved outcomes with greater protein-calorie ingestion. Until the links between these surrogate markers of nutrition and inflammation are better described in terms of their association with outcomes, and it is clearly demonstrated that they can be improved through intervention (ie, are “actionable”), establishing them as benchmarks and testing strategies for their improvement would be inappropriate.

Summary

The practice of evidence-based medicine utilizes the current best evidence in making decisions about the care of individual patients. In providing medical care for ESRD patients, several aspects of their care, including dosing of dialysis, anemia management, and diagnosis and treatment of
malnutrition, must be addressed simultaneously. The renal community has utilized its large clinical databases to perform retrospective cohort studies and draw conclusions about the associations between clinical care and mortality. In the cases of dialysis dose and anemia correction, conclusions were translated into clinical benchmarks in an effort to improve delivery of care. Subsequently, the observations from these retrospective studies were used to formulate clinical questions and design prospective treatment trials to provide additional evidence to guide therapy. Additional research needs to be performed using this as a paradigm to understand the association between nutrition and mortality, define the appropriate benchmark, and identify the treatment strategy to test. While this template or process could be easily translated to other aspects in the evaluation and creation of evidence to guide clinical practice in the care of ESRD patients, it should also be considered in the development of evidence-based guidelines for other patient populations.

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References


Figure 4. Odds ratios for death for a range of urea reduction ratios and serum albumin concentrations in 13,473 patients with end-stage renal disease treated with hemodialysis. NS = not significant. (Adapted with permission from Owen WF, Lew NL, Liu Y, Lowrie EG, Lazarus JM. The urea reduction ratio and serum albumin concentration as predictors of mortality among patients undergoing hemodialysis. N Engl J Med 1993;329:1001–6.)
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