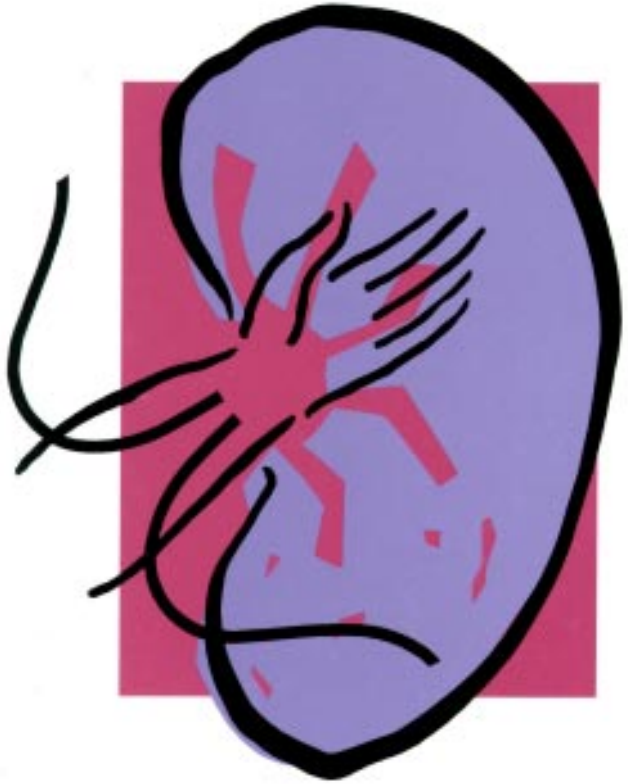


NIH Consensus Statement

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Morbidity and Mortality of Dialysis

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This statement reflects the panel's assessment of medical knowledge available at the time the statement was written. Thus, it provides a "snapshot in time" of the state of knowledge on the conference topic. When reading the statement, keep in mind that new knowledge is inevitably accumulating through medical research.

Abstract

The National Institutes of Health Consensus Development Conference on Morbidity and Mortality of Dialysis brought together experts in general medicine, nephrology, pediatrics, biostatistics, and nutrition as well as the public to address the following questions: (1) How does early medical intervention in predialysis patients influence morbidity and mortality? (2) What is the relationship between delivered dialysis dose and morbidity/mortality? (3) Can co-morbid conditions be altered by non-dialytic interventions to improve morbidity/mortality in dialysis patients? (4) How can dialysis-related complications be reduced? and (5) What are the future directions for research in dialysis? Following 1½ days of presentations by experts and discussion by the audience, a consensus panel weighed the evidence and prepared their consensus statement.

Among their findings, the consensus panel concluded that (1) patients in the predialysis phase, including children, should be referred to a renal team in an effort to reduce the morbidity and mortality incurred both during the predialysis period and when receiving subsequent dialysis therapy; (2) the social and psychological welfare and the quality of life of the dialysis patient are favorably influenced by the early predialytic and continued involvement of a multidisciplinary renal team; (3) attempts should be made to avoid a catastrophic onset of dialysis by instituting predialytic intervention and the appropriate initiation of dialysis access; (4) quantitative methods now available to objectively evaluate the relationship between delivered dose of dialysis and patient morbidity and mortality suggest that the dose of hemodialysis and peritoneal dialysis has been suboptimal for many patients in the United States; (5) factors contributing to underdialysis of some patients include problems with vascular and peritoneal access, nonadherence to dialysis prescription, and underprescription of the dialysis dose; (6) cardiovascular mortality accounts for approximately 50 percent of deaths in dialysis patients, and relative risk factors such as hypertension, smoking, and chronic anemia should be treated as soon as possible after diagnosis of chronic renal failure; (7) early detection and treatment of malnutrition contribute to improved survival of patients on

dialysis; and (8) until prospective, randomized, controlled trials have been completed, a delivered hemodialysis dose at least equal to a measured fractional urea clearance of $K_{dr}t/V$ of 1.2 (single pool) and a delivered peritoneal dialysis dose at least equal to a measured $K_{pr}t/V$ of 1.7 (weekly) are recommended.

The full text of the consensus panel's statement follows.

Introduction

Prior to 1960, end-stage renal disease (ESRD) was uniformly fatal. However, with the development by Wayne Quinton and Belding Scribner of an external shunt to provide repeated vascular access coupled with the use of dialysis technology that had evolved some years earlier for the treatment of acute renal failure, chronic intermittent hemodialysis for the management of ESRD was launched in March 1960 at the University of Washington. The application of peritoneal dialysis for the management of ESRD soon followed. A little over a decade elapsed before Congress legislated the provision of Medicare coverage, regardless of the patient's age, for the treatment of ESRD. These as well as subsequent events have made it possible for hundreds of thousands of patients with ESRD to receive life-sustaining renal replacement therapy.

The incidence of treated ESRD in the United States is 180 per million population and continues to rise at a rate of 7.8 percent per year. In 1990, over 45,000 new patients were enrolled in the Medicare ESRD program, of which 66 percent were white, 28 percent were African Americans, 2 percent represented Asians/Pacific Islanders, and 1 percent were Native Americans. Of these patients, 43 percent were at least 64 years of age, and fewer than 2 percent were under 20 years of age. On average, African Americans and Native Americans are younger at the onset of treated ESRD and show dramatically higher incidence rates than do whites or Asians/Pacific Islanders. Although clinical experience suggests that the incidence of ESRD in Hispanics is also greater than in whites, data from the United States Renal Data System are not available to confirm this clinical impression. Hypertension and diabetes accounted for 63 percent of the new cases in 1990. The incidence of diabetic ESRD in Native Americans was almost twice that of African Americans and six times that of whites.

Of the more than 195,000 ESRD patients receiving renal replacement therapy during 1990, 70 percent were being treated with either hemodialysis or peritoneal dialysis. Although kidney transplantation is the treatment of choice for many patients with ESRD, the increase in waiting time for cadaveric organs, the presence of disqualifying co-morbid

conditions, and the low transplantation rates in an aging ESRD population will likely ensure that dialysis remains the primary method of renal replacement therapy in the foreseeable future.

The cost for care of patients with ESRD from all sources including Federal, State, and private funding was approximately \$7.26 billion in 1990, an increase of 21 percent over a similar estimate for the preceding year. Not reflected in this figure are additional expenditures for outpatient drugs and supplies, the cost of disability, and Social Security payments. As the U.S. population continues to grow and a larger proportion of the population at risk attains the age of 65 and beyond, the cost of kidney disease including this end-stage component is projected to increase. According to an analysis conducted by the Health Care Financing Administration, by the turn of the century it is estimated that more than 300,000 patients will be enrolled in the ESRD program. Furthermore, 85,000 new patients will enter the program in the year 2000 alone. Most of the increase will come from the aged and the diabetic population.

Despite improvements in dialysis technology over the past decade, mortality in the ESRD population remains high. For instance, at age 49 the expected duration of life of an ESRD patient is 7 years compared with approximately 30 years for an individual of the same age from the general population. In addition to increased mortality, patients with ESRD also experience significantly greater morbidity, including a substantial loss in quality of life. In 1986, for example, for all Medicare patients over 65 years of age, hospitalization averaged 2.8 days per year, whereas for those after 1 year on dialysis the median number was 15.0 days per year. The relevant information available to prescribe the appropriate dialysis dose is limited and subject to gross errors. As a consequence, "What is an adequate dialysis dose?" remains a controversial question among professionals caring for patients on dialysis.

To resolve questions concerning delivered dialysis dose, as well as co-morbid conditions and dialysis-related complications, all of which appear to cause increased morbidity and mortality in the United States dialysis population when compared with certain European countries and Japan, the National Institute of Diabetes and Digestive and Kidney Diseases and

the Office of Medical Applications of Research of the NIH convened a Consensus Development Conference November 1-3, 1993. Following 1-1/2 days of testimony by experts in the field, a consensus panel representing the professional fields of general medicine, nephrology, pediatrics, biostatistics, nutrition, and nursing, and a representative of the public considered evidence and agreed on answers to the questions that follow.

- How does early medical intervention in predialysis patients influence morbidity and mortality?
- What is the relationship between delivered dialysis dose and morbidity/mortality?
- Can co-morbid conditions be altered by nondialytic interventions to improve morbidity/mortality in dialysis patients?
- How can dialysis-related complications be reduced?
- What are the future directions for research in dialysis?

How Does Early Medical Intervention in Predialysis Patients Influence Morbidity and Mortality?

It is clear that factors influencing the morbidity and mortality in dialysis patients are operative for an extended period before ESRD is present and the need for dialysis is imminent. Unfortunately, only a minority of patients (20 to 25 percent) are referred to a renal physician prior to the initiation of dialysis. Managed care programs must recognize the importance of the continued involvement of the renal team in the care of these patients. A number of conditions related to renal failure are present prior to the onset of dialysis including anemia, hypertension, malnutrition, renal osteodystrophy, lipid abnormalities, and metabolic acidosis. In addition, smoking and poor glycemic control in diabetics will influence subsequent morbidity and mortality. The costs of delayed referral include both emergency dialysis, with its higher morbidity and mortality, and excessive utilization of health care dollars. Emergency dialysis jeopardizes the choice for modality of dialysis, endangers the ability to maintain prolonged vascular access, precludes psychological preparation of the patient for ESRD care, and necessitates hospitalization for a catastrophic complex illness. The mortality in this crisis situation can be as high as 25 percent.

In the patient with progressing renal insufficiency, early intervention should be aimed at reversal of hypertension and correction of identified nutritional deficiencies and acidosis. While data are limited, the use of erythropoietin will prevent severe anemia and may reverse its associated complications. There is no consensus on the ultimate role of dietary protein restriction in slowing the progression of renal failure. However, an intake level of 0.7 to 0.8 g/kg/day can maintain nutritional status in noncatabolic patients with ESRD without placing an undue burden on the capacity to eliminate potentially toxic metabolites including acid, potassium, sulfate, phosphorus, magnesium, and unidentified uremic toxins. Because of deleterious effects of parathyroid hormone, therapies aimed at prevention or reversal of secondary hyperparathyroidism should be initiated in the predialysis phase.

Referral of a patient to a renal team should occur when the serum creatinine has increased to 1.5 mg/dL in women and 2.0 mg/dL in men. Predialysis referral to a renal team, consisting of a nephrologist, dietitian, nurse, social worker, and mental health professional, allows time to establish a working relationship, to acquaint the patient with the various modes of renal replacement therapy, and to provide information on dialysis access, nutritional modification, avoidance of potentially nephrotoxic drugs, and potential financial support for services. It is essential to initiate the medical interventions, discussed below, to reduce mortality and morbidity as soon as possible.

Hypertension

Increasing evidence suggests that aggressive therapy of hypertension in the predialysis period delays progression of renal disease and is the most potent intervention to decrease subsequent cardiovascular mortality in dialysis patients. As in patients without renal disease, hypertension is the most important etiologic factor in the development of left ventricular hypertrophy (LVH) and diastolic dysfunction. It has been proposed that delay of adequate therapy or failure to lower blood pressure to normal over several years results in changes that become irreversible or only slowly reversible on dialysis. Hypertension is the highest risk factor for coronary artery disease and cerebral vascular disease. The goal of therapy is a normal systolic and diastolic pressure.

Anemia

Studies now suggest that aggressive treatment of anemia is as important in the predialysis period as during dialysis. In fact, to reduce cardiovascular morbidity and mortality, predialysis therapy may be critical, since longstanding LVH associated with anemia may be poorly reversible or irreversible if therapy is delayed until the commencement of dialysis. In addition, predialysis correction of anemia appears to improve or maintain functional capacity, nutritional adequacy, sexual function, and psychological health. It also reduces the risk of hepatitis and sensitization to transplant antigens associated with transfusion. As in the dialysis patient, the predialysis patient

should be evaluated for other causes of anemia besides the renal failure, and any nutritional deficiencies should be corrected. As the anemia worsens, the physician should initiate therapy with subcutaneous erythropoietin. The target hematocrit has not yet been determined. At present, it is recommended that the hematocrit be maintained above 30 percent, but studies are now being conducted to determine if higher hematocrit levels produce better results.

Renal Osteodystrophy

It is known that the factors mediating renal osteodystrophy are present early in the course of progressive renal disease. These factors need to be managed throughout the entire predialysis course to prevent the ravages of severe, potentially irreversible hyperparathyroidism. Patients should be instructed early in dietary phosphate restriction, probably before the serum phosphate is elevated. Calcium-containing phosphate binders should be initiated when minimal elevations of phosphate are evident. Metabolic acidosis should be rigorously treated to maintain bicarbonate near or at the normal range because of the effect of acidosis in increasing bone dissolution and inhibiting osteoblastic activity, especially in children and women. Treatment of acidosis may also improve protein metabolism.

Nutritional Therapy

At an early meeting with the renal team, a nutritional assessment by a trained dietitian should be accomplished and should include as a minimum weight, height, recent weight loss, upper arm anthropometry, and serum proteins (albumin, transferrin, and/or prealbumin). In the absence of obvious malnutrition a modest protein-restricted diet of 0.7 to 0.8 g of protein/kg/day will provide good nutrition. When malnutrition is present, emphasis on adequate caloric intake, greater amounts of dietary protein of up to 1 to 1.2 g/kg are called for in order to allow nutritional repletion or to counter the catabolic effects of stress. Measurement of urinary urea nitrogen to assess net protein catabolic rate (PCR) can be useful for monitoring protein intake. In certain patients in the predialysis period, fluid retentive states will make nutritional assessment more difficult. Newer techniques such as multifrequency

bioimpedance analysis and dual emission x-ray absorptiometry offer promise for ease, reproducibility, and accuracy for assessing states of fluid overload and bone mineral status, respectively.

The dietitian should also design dietary prescriptions for energy, fat and carbohydrate, fluid, sodium, and phosphate, as well as other micronutrients, recognizing that the adequacy of energy intake will be largely monitored by weight change in outpatients. Although modification of the diet to minimize lipid abnormalities is reasonable, such modifications should not be so rigid that they limit energy intake below daily requirements. Lipid abnormalities, particularly hypertriglyceridemia and reduced high density lipoprotein (HDL) cholesterol along with elevations in lipoprotein(a), are common in ESRD, but there are limited data supporting the efficacy of diet or drug therapy, and there is some evidence that the drugs usually employed have more serious side effects.

Quality of Life

Quality of life is very important in the predialysis period and should be given strong consideration in the decision to initiate dialysis. Maintenance of physical strength, appetite, and sense of well-being, as well as optimal physiologic functioning promotes interpersonal relationships with family and friends as well as rehabilitation and job retention in the working patient. As the likely need for dialysis approaches, preparation of the patient by introduction to various aspects of the therapy, to members of the renal team, and to the physical site of the therapy as well as to other patients undergoing dialysis will generally facilitate acceptance and compliance. Another potential benefit is the opportunity to discuss the characteristics of the various modes of the therapy in order to involve the patient in this selection and to allow early placement of vascular access if hemodialysis is the method chosen.

Dialysis Access

The benefits of early establishment of vascular access should be emphasized. Arteriovenous (A-V) fistula surgery must occur weeks to months before the initiation of dialysis to permit maturation of the fistula. Likewise, a peritoneal dialysis catheter

should be placed at least 1 month prior to its anticipated use. There may exist advantages to newer catheters in which the external segment is initially buried subcutaneously and exteriorized when needed at a later date. Late referral is clearly associated with increased complications, the need for emergency hemodialysis, and possible long-term access problems.

Interventions in Renal Failure in Childhood

Chronic renal failure is different in childhood than in adults in that its incidence is low (11 per 10⁶ per year) and its causes are obstructive uropathy, renal dysplasia, and congenital or inherited diseases in a majority of cases. Morbidities associated with childhood chronic renal failure are growth failure, osteodystrophy with bone deformity, salt and water losses due to urologic abnormalities, and neurologic abnormalities, including seizures, deafness, retardation, and learning disabilities. Because of growth requirements, dietary protein intake should be higher than for adults, perhaps as high as 1.3 to 1.5 g/kg/day or even higher for children receiving peritoneal dialysis. The production of erythropoietin and calcitriol and the functions of the growth-hormone-IGF-1 axis may be impaired from birth onward. Because of these features, predialysis therapy should be aimed at correcting malnutrition, hormone deficiencies, salt depletion, and neurologic dysfunction.

What Is the Relationship Between Delivered Dialysis Dose and Morbidity/Mortality?

Hemodialysis

Indices of hemodialysis adequacy have historically included measurements of serum creatinine and urea, estimates of dialysis delivery (square meter-hour), and assessment of patient well-being.

Recently, an estimate of fractional urea clearance during dialysis has been suggested as a more quantifiable measurement of dialysis efficacy. This estimate uses urea as a marker for uremic toxins cleared during the dialysis procedure. The fractional urea clearance model for delivered hemodialysis dose is expressed as $K_{\text{dr}}t/V$, where K_{d} is dialyzer clearance (mL/min), r is residual renal urea clearance (mL/min), t is treatment time (min), and V is total-body urea distribution volume in a single pool (mL). A simpler and more common measurement of fractional urea clearance during a single dialysis treatment is the urea reduction ratio (URR). This ratio is expressed as a percentage and is calculated as $[(\text{predialysis BUN} - \text{postdialysis BUN})/\text{predialysis BUN}] \times 100$. An approximate relationship between these two means of expressing dialysis dose can be made: $K_{\text{dr}}t/V$ of 1.2 is approximately equal to URR 60 percent. Although urea may be distributed in multiple body pools, most current measurements use a single-pool model to calculate urea clearance.

Recent reports demonstrated a direct correlation between dialysis mortality and $K_{\text{dr}}t/V$ (or URR). Several studies have also suggested that the dialysis dose delivered to many hemodialysis patients in the United States was less than that recommended by the National Cooperative Dialysis Study. Although data from controlled, prospective studies are not available, retrospective data presented and opinions expressed at the consensus conference favor a recommendation for a minimum delivered hemodialysis (conventional dialyzer, single urea pool analysis) of $K_{\text{dr}}t/V$ of 1.2 in patients with protein intake of approximately 1.0 to 1.2 g/kg/day. It is suggested that assessment of dialysis dose, by formal $K_{\text{dr}}t/V$ modeling, be performed on a regular basis. Opinions were

expressed that dialysis time may be an independent predictor of mortality irrespective of the dialyzer urea clearance. It is obvious that a prospective, randomized, controlled study relating the dose of delivered dialysis to morbidity and mortality is of great importance.

In the metabolically stable patient, net protein catabolic rate reflects protein intake. Since changes in $K_{\text{dr}} t/V$ may be paralleled by corresponding changes in net protein catabolic rate, dietary protein intake may decrease if the dialysis prescription fails to achieve the desired goal and the patient becomes symptomatic.

Morbidity

Attainment of the recommended $K_{\text{dr}} t/V$ is influenced by a number of factors, modifiable and unmodifiable, which may alter the delivered dose. These include, but are not limited to, the following:

Vascular access: Obstruction to blood flow in the vascular access may occur and result in recirculation of blood through the dialysis circuit, thereby contributing to decreased dialysis.

Equipment: Blood flow rate and dialyzer surface area and mass-transfer coefficient must be considered to give optimal delivery to achieve the calculated dialysis dose. Effective dialyzer surface area must be carefully monitored because excessive reuse of dialysis membranes results in loss of dialyzer efficiency and reduction of the delivered dialysis dose.

Patient factors: Adherence to salt and water intake limitations must be met to avoid unnecessary fluctuations in blood volume during hemodialysis and the associated loss of effective dialysis. Other patient compliance issues include adherence to appointment schedules and time on dialysis. Patients with certain underlying diseases (e.g., diabetes, amyloidosis, drug dependence) have special problems that may interfere with dialysis.

Dialysis Biocompatibility

The composition of the hemodialyzer membrane may be a factor in establishing urea clearance goals, i.e., biocompatible polymer membranes such as polysulfones, polyacrylonitrile, and polymethylmethacrylate have permeability characteristics different from cellulosic membranes. In addition, the composition of the membrane may be a factor in the nature and intensity of the interaction between the membrane and blood. Generally, cellulosic-based membranes, in contrast to the more biocompatible membranes, have a greater capacity to activate complement and to attenuate the granulocyte response. It has also been suggested that the use of biocompatible membranes may result in lower mortality rates.

Peritoneal Dialysis

Peritoneal dialysis utilizes a natural membrane to remove nitrogenous products from the body fluids of individuals with impaired renal function. The use of relatively long dwell-time peritoneal exchanges [continuous ambulatory peritoneal dialysis (CAPD)] has enabled individuals to carry on normal daily activities without the use of machines or other appliances. The dose of peritoneal dialysis has been established empirically and depends to some extent on patient acceptance of frequent interruptions for the exchange of peritoneal fluid. Recently, an effort has been made to prescribe for each individual patient the dose of peritoneal dialysis needed to attain target levels of urea clearance. In general, four exchanges of 2 liters each may generate as much as 10 liters of dialysate (allowing for the removal of ultrafiltrate). Assuming nearly complete equilibration of urea between plasma and peritoneal fluid, this equates to a weekly urea clearance of approximately 70 liters. For a 70-kg man with a urea “space” of 42 liters, the calculated delivered peritoneal dialysis dose, $K_{pr} t/V$, is 1.7. The weight of current evidence indicates that this value of $K_{pr} t/V$, is a reasonable minimal delivered dose for most functionally anephric CAPD patients who daily eat approximately 0.9 to 1.0 g/kg of protein. The dose of nighttime peritoneal dialysis is usually increased above that of CAPD.

The prescription of dialysis will depend on the volume of urea distribution, the efficiency of peritoneal exchange, and the residual renal urea clearance.

Peritoneal dialysis is a demanding and time-consuming therapy. Omission of exchanges or shortening exchange times by the patient will reduce urea clearance and lead to increased morbidity and mortality. The use of urea as an index of peritoneal dialysis efficiency is complicated, because the peritoneal membrane is more permeable to large molecules than are dialyzer membranes.

Peritoneal dialysis efficiency can be increased by more frequent exchange (5/day), increased volume per exchange (2.5 to 3.0 liters), and the coupling of CAPD with nighttime cycler dialysis in large individuals or those with relatively low peritoneal clearances.

Children

Children undergoing chronic dialysis therapy are more likely to receive peritoneal dialysis than adults. This preference is based on technical factors including problems maintaining chronic hemodialysis access. Because of the serious problems of growth failure and neurologic dysfunction, children require appropriate hormone therapy (erythropoietin, calcitriol, and growth hormone), nutrition support services, and neurologic evaluation. A qualified pediatric nephrologist is an essential member of the renal team. Data indicate that intervention with specified nutrition, growth hormone, erythropoietin and calcitriol therapy, and avoidance of aluminum can clearly improve growth velocity. Because of the serious problems of growth failure and neurologic dysfunction, children with renal insufficiency should be referred to centers with specialized pediatric nephrologic care. Children also require educational and play facilities at the dialysis center.

Children of all ages with ESRD benefit from treatment with peritoneal and hemodialysis. The principles of dialysis outlined for adults generally hold for children, although no retrospective or prospective studies have been performed that indicate reasonable targets of $K_{pr}t/V$ or $K_{cr}t/V$ to maximally allay morbidity and mortality.

Children with chronic renal failure suffer from a cycle of depression, anxiety, and loss of self-esteem. The difficulties encountered often result in family stress with a high divorce rate among the parents of children undergoing dialysis. For these reasons, a mental health professional is an essential component of the pediatric renal disease center.

Finally, dialysis should be a temporary therapy, since renal transplantation is considered the treatment of choice for children.

Can Co-Morbid Conditions Be Altered by Nondialytic Interventions To Improve Morbidity/Mortality in Dialysis Patients?

Cardiovascular Abnormalities

Cardiovascular events (principally systolic and diastolic dysfunction, myocardial infarction, and stroke) account for 50 percent of the mortality in dialysis patients, and also contribute importantly to mortality after renal transplantation.

Studies of patients entering dialysis treatment demonstrate a high prevalence of established cardiovascular abnormalities including hypertension, LVH, coronary artery disease, and cardiac failure. For example, two-dimensional echocardiograms are abnormal in 70 percent of such patients. The rising mean age of dialysis patients likely will further increase this cardiovascular pathology.

We believe that optimum reduction of dialysis morbidity and mortality begins with predialysis intervention. The patient with chronic renal failure is at high risk for cardiovascular events. It is likely, but not yet proven, that prevention of severe anemia by erythropoietin will also prevent, diminish, or partially reverse left ventricular overload.

Cessation of smoking, correction of obesity, and regular aerobic exercise may also contribute to reducing mortality from cardiovascular disease. Normotension and nonsmoking have been two characteristics of 20-year-plus survivors on chronic dialysis.

It is not yet known whether modifications of the common lipid abnormalities in chronic renal failure and ESRD patients can be safely achieved in the long term by currently available lipid-lowering agents or whether this would be beneficial.

Because myocardial calcification and fibrosis may contribute especially to diastolic dysfunction (which accounts for 50 percent of cardiac failure in dialysis patients) control of calcium, phosphorus, and parathyroid hormone levels may help to prevent cardiovascular disease as well as bone disease.

Two-thirds of ESRD is due to two primary diseases--diabetes mellitus and essential hypertension--that themselves contribute importantly to cardiovascular disease. Not infrequently, such patients have had erratic treatment and followup programs prior to the onset of chronic renal disease. The identification of a diabetic patient has not routinely led to inclusion of that patient in a program of strict glycemic control and followup of potential microvascular and renal complications, such as micro or gross albuminuria. We also now understand that careful control of blood pressure upon diagnosis of diabetes mellitus is crucial.

Current studies suggest that blood pressure is not being adequately controlled in many dialysis patients. Blood pressure at the initiation of each dialysis treatment should be in the normal range or as near as possible to it. Adequate ultrafiltration and restriction of interdialytic intake of sodium chloride should establish normotension in up to 80 percent of dialysis patients. Mechanisms of hypertension in the remainder include an inappropriately hyperactive renin-angiotensin system, nephrogenic activation of the sympathetic nervous system and, possibly, an altered balance of endothelial factors (nitric oxide and endothelin) influencing arteriolar smooth muscle tone.

Nutritional Deficiency

The nutritional status of the patient is a major factor in the outcome of hemodialysis treatment and may be maintained in the predialysis period by the use of low-protein diets in the range of 0.7 to 0.8 g/kg/day together with adequate calorie intake of 35 kcal/kg/day. It is essential that during this period, malnutrition, as evidenced by a decrease in albumin and body weight, is not allowed to develop in renal patients. Serum albumin levels above 3.5 g/dL are associated with little mortality, while mortality rises dramatically with lower values for serum albumin.

Once the patient is on hemodialysis, dietary protein should be liberalized to equal 1.0 g/kg/day, with appropriate calorie supplementation, to sustain nutrition at a normal level. The complexity of nutritional intervention for the renal patient is of

such degree and, at the same time, of such importance as to require the expert guidance of a well-trained renal dietitian. High cholesterol is indicative of increased risk of morbidity and mortality, but values below 100 mg/dL are also associated with increased mortality. The reasons why hypoalbuminemia and hypocholesterolemia are indexes of high mortality are not known.

Educational programs instituted by the renal center and by organizations concerned with the welfare of all kidney patients should explain the need for adequate dialysis time and correction of malnutrition, because these factors contribute to longer life of higher quality, and correction of many co-morbid conditions. Patient participation, as an integral part of the renal team, is of the essence if success in improving quality of life is to be achieved.

Current concerns about morbidity and mortality raise issues regarding the present uniform reimbursement system for dialysis, especially in the area of nutritional and psychosocial support systems. Linking direct reimbursement for such care to important outcomes such as levels of serum albumin, mean blood pressure, and measurements of fractional urea clearance during dialysis should be explored.

How Can Dialysis-Related Complications Be Reduced?

Although dialysis allows effective and productive lives for many patients with ESRD, a variety of complications can occur. Problems with dialysis access, infections, atherosclerosis and cardiovascular disease, malnutrition, and metabolic abnormalities, as well as persisting uremic symptoms and acute symptoms related to the dialysis procedure itself, may limit a patient's health and quality of life. Disorders of calcium, phosphorus, vitamin D, and parathyroid hormone are common and may be disabling.

Hemodialysis

Perhaps the major complication limiting continued effective hemodialysis involves vascular access. The most effective, durable access is the A-V fistula. Unfortunately a satisfactory fistula cannot be established in many patients, because of inadequate vessels (especially in diabetic patients). The chances of a successful fistula are enhanced by early planning and placement well before dialysis becomes necessary. When early planning is not possible, the use of a tunneled subcutaneous catheter may make dialysis possible while an A-V fistula is maturing, but repeated use of temporary subclavian catheters is often accompanied by infection or thrombosis, with ultimate impairment of subclavian flow and loss of the whole arm for dialysis access purposes. Use of temporary catheters should be avoided when possible.

When a fistula is unsuccessful or not feasible, a synthetic graft is ordinarily placed. Current experience indicates that 60 percent of these grafts fail each year due to thrombosis. Anatomic stenosis is responsible for 80 percent of these clots (almost all are on the venous side of the anastomosis) while the rest result from other causes such as excessive post-venepuncture pressure by manual compression or clamp or sleeping on the graft. Medical thrombolysis may remove the clot and restore flow, but often surgical thrombectomy is required. The stenosis, usually formed by endothelial proliferation, sometimes responds to percutaneous angioplasty but may require surgical intervention. The present life of a synthetic graft is about 2 years with loss due to thrombosis in 80 percent and infection in 20 percent of patients.

Consistently elevated venous dialysis pressure may provide a warning of developing stenosis and hence of impending thrombosis and may indicate the need for a fistulogram. An increase in recirculation may also indicate an incipient problem. Attention to these signs may allow for intervention prior to clotting of the graft and prevent its loss.

The need for meticulous, experienced surgical skill in establishing satisfactory fistulas and shunts must be emphasized. Although the procedure may not be dramatic, a dialysis patient's life often depends on the presence of a reliable access. Nursing skill in access use has a major influence on dialysis success.

Infection

Infection remains the major cause of death in 15 to 30 percent of all dialysis patients; a figure that has not changed significantly over the years. Infections are usually due to common organisms and often appear to be access-related. About 60 percent of bacteremic infections are Gram-positive, especially *Staphylococcus aureus*. Perhaps 50 to 60 percent of dialysis patients are carriers of this organism (compared with 10 to 30 percent of the general population), and the carrier rate among diabetic patients is still higher. It is possible to reduce the carrier rate with prophylactic antibiotic treatment, but this may encourage the emergence of resistant organisms.

Uremia itself causes an impairment in cell-mediated immunity that is not totally corrected by dialysis. In addition, granulocyte phagocytosis and killing functions appear to be impaired by cellulosic dialysis membranes. Biocompatible membranes may have fewer deleterious effects on white cell function and other defense mechanisms. Some studies suggest a 50 percent fall in incidence of infection accompanying a switch to more biocompatible dialyzers.

Peritoneal Dialysis

The overwhelming cause of unsuccessful peritoneal dialysis is peritonitis. Although improvement has followed recent changes in tubing and connection systems, recurrent peritonitis is a continuing problem for many patients. Catheter tunnel

infection often underlies this peritonitis, and changes in catheter design (e.g., U shape), placement (with both peritoneal and skin ends directed caudad and a cuff placed in the rectus muscle), and the use of prophylactic antibiotics at the time of placement or thereafter have been proposed as deterrents to infection. The use of vaccine against *Staphylococcus* organisms and of bacteriostatics such as silver-coated catheters is under investigation.

Calcium, Phosphorus, and Parathyroid Hormone

The disturbances in body calcium, phosphorus, vitamin D, parathyroid hormone, and bone disease that usually start prior to the initiation of dialysis continue to demand consistent attention so long as dialysis is required. Mainstays in therapy include control of dietary phosphorus, minimization of its absorption by use of phosphate-binders, and the use of calcitriol. Control of dietary intake of phosphorus requires patient education by the renal team and adherence by the patient to the recommended diet. Previous reliance on aluminum hydroxide to prevent absorption of phosphorus has been largely discontinued because of accumulation of aluminum in the brain and bone, leading to severe neurological disorders and osteomalacia. Ingestion of calcium carbonate or calcium acetate with meals is currently recommended for most patients to prevent absorption of phosphorus. Use of these calcium salts may require adjustments in the concentration of calcium in the dialysate fluid to prevent hypercalcemia and consequent deposition of calcium phosphate salts with damage to the heart, blood vessels, and other tissues. Careful titration of the calcitriol dosage is required to obtain its benefits without causing hyperphosphatemia or hypercalcemia. Careful attention to dietary phosphorus, calcium salts, and calcitriol often enables parathyroid hormone concentrations to be maintained at or near normal. Of serious concern is the emergence of “adynamic bone disease,” a condition diagnosed by bone biopsy in which the normal correction of bone wear and tear by “remodeling” fails to occur. The exact cause(s) and consequences of adynamic bone disease are not yet known.

Amyloid

Amyloidosis in dialysis patients is associated with long-term (>6 years) dialysis, and is increased in frequency in older patients. The deposition of beta-2-microglobulin protein as amyloid causes carpal tunnel syndrome, destructive arthropathy in medium- and large-sized joints, and cystic bone disease. The disorder may be due both to increased release of beta-2-microglobulin from macrophages and, significantly, to reduction in the destruction of beta-2-microglobulin that normally occurs in functioning kidneys. Some evidence indicates that amyloidosis is a lesser problem in patients dialyzed with high-flux membranes than in those with cellulosic membranes, perhaps because of both decreased release of the protein from macrophages and from partial removal of the protein during dialysis by filtration or binding with some synthetic polymer membranes. Serious consideration should be given to the use of these membranes for dialysis of patients in whom amyloidosis is a problem or may become a clinical concern.

Anemia

Attention to the management of anemia, begun in the predialysis phase of care, must be continued into dialysis.

Intradialytic Complications

Acute complications related to the dialysis procedure itself may severely compromise the quality of life in chronic dialysis patients. A mild degree of hypotension is “normal” in dialysis, but severe degrees may be disabling. Muscle cramps, chest or back pain, hypoxemia, fever, nausea, seizures, or cardiac arrhythmias may occur. In addition, mechanical problems related to dialysis machines, cartridges, and water purifiers may occur.

Some of these problems have been lessened by the use of bicarbonate rather than acetate dialysis solutions, by longer dialysis periods with lower rates of ultrafiltration, by the use of synthetic polymer dialysis membranes that are biocompatible, and perhaps by reuse of these membranes. Reuse brings the potential for problems as well as benefits; however, additional

research will be necessary to define the optimum mix of membranes, reuse, solutions, and time and intensity of dialysis to ensure maximum safety and minimum complications of dialysis.

Psychosocial Concerns

Early predialysis assessment and continuous, active intervention by the renal team, including mental health professionals, in the care of a patient beginning dialysis are more likely to be effective than efforts initiated later in treatment. This assessment should include measures of quality of life and social role function in addition to lack of mental acuity and depression. Ensuring patients' understanding and positive participation in their care is a primary goal of this intervention in addition to optimizing the relationship between patient and physician and patient with staff. The earlier this assessment is accomplished the greater will be the potential for a positive impact on physical and social rehabilitation. Exercise and physical training can add to physical well-being and should also be initiated at the beginning of dialysis, or in the predialysis period.

What Are the Future Directions for Research in Dialysis?

- Studies should be conducted to evaluate the effect of aggressive nutritional support in malnourished predialysis patients, to determine the mechanisms by which malnutrition increases mortality and morbidity rates, and to develop sensitive and specific methodology to detect the early stages of malnutrition.
- Studies should be instituted to determine the benefits and risks of early control of renal osteodystrophy on morbidity and to explore the causes and therapy of disturbances in calcium, phosphorus, and vitamin D, both at the basic level on regulation of bone metabolism and at the clinical level on the importance of soft tissue calcium deposition. Studies should include development of new phosphate-binding agents and noncalcemic analogues of vitamin D, and determination of the optimal degree of suppression of parathyroid hormone.
- Basic and clinical studies should be initiated to evaluate the effect of chronic uremia on neurologic function.
- Basic and clinical studies should be conducted to evaluate the effect of uremia on growth in children.
- Studies should be initiated to determine the impact of early treatment of anemia on mortality, morbidity, and rehabilitation. Studies to determine when to initiate treatment of anemia and what the target hematocrit should be are needed in both the predialysis and the dialysis patient.
- A prospective, randomized, controlled clinical trial should be initiated to examine the differences in patient morbidity and mortality at $K_{cr,t}/V$ levels of 1.2 (single pool) and 1.6 for hemodialysis patients.
- A prospective, randomized, controlled clinical trial should be initiated to examine the differences in patient morbidity and mortality at delivered weekly $K_{pr,t}/V$ levels of 1.47 and 2.10 in peritoneal dialysis patients.

- A prospective, randomized, controlled clinical trial, at a specified level of delivered dialysis dose, should be initiated to determine the differences in the effects of biocompatible, high-flux versus cellulosic membranes in studies which include, but are not limited to, patient survival, incidence of infection, and incidence and course of beta-2-microglobulin amyloidosis.
- Additional studies to establish the effect of reuse of dialysis membranes on hemodialysis effectiveness and morbidity and mortality are recommended.
- A prospective study of the feasibility and effectiveness of modification of cardiovascular risk factors in chronic renal failure patients both before and after initiation of dialysis should be undertaken. Risk factors to be evaluated would include hypertension (mechanism of development and regression of left ventricular hypertrophy and characterization of the best pharmacological approaches to antihypertensive treatment), smoking, obesity, and uremic dyslipidemia. The role of metabolic factors such as hyperinsulinemia and parathyroid hormone and calcium-phosphorus relationships including tissue calcium burden in the myocardium and methods of its detection should be examined. Finally, development of noninvasive testing for coronary artery disease in this patient population should be explored.
- Studies to determine the mechanisms of interdialytic hypertension should be initiated and should include the respective roles of abnormal renin-angiotensin responses, abnormal thirst and salt craving, vascular endothelial factors (endothelin, nitric oxide production, and inhibitors), the renal-sympathetic axis, the relationship to erythropoietin administration, and the role for continuous blood pressure monitoring.
- Studies of the mechanisms by which malnutrition increases mortality and morbidity rates due to infections, anorexia, hypogusia, and related problems in the dialysis patient should be undertaken.

- Improved methods for detecting stenosis and thrombosis of access grafts and understanding the mechanism of endothelial proliferation leading to vascular graft stenosis are needed. Improved materials and techniques should be developed to diminish access clotting and infection and new methods identified for cost-effective thrombolysis in clotted grafts.
- Study of the immunodeficiency of uremia and evaluation of antibacterial vaccines, antibiotic prophylaxis, and dialyzer membrane characteristics in the prevention of infection in dialysis patients should be initiated.
- Evaluating and standardizing methods for measurement of psychological well-being and quality of life in dialysis patients, and applying these instruments in studies on the effectiveness of interventions should be undertaken.

Conclusions

- Patients, including children, in the predialysis phase should be referred to a renal team consisting of a nephrologist, dietitian, nurse, social worker, and mental health professional in an effort to reduce the morbidity and mortality incurred both during the predialysis period and when receiving the subsequent dialysis therapy.
- The social and psychological welfare and the quality of life of the dialysis patient are favorably influenced by early predialytic and continued involvement of a multidisciplinary renal team.
- Attempts should be made through predialytic intervention and the appropriate initiation of dialysis access to avoid a catastrophic onset of dialysis.
- Quantitative methods to measure the delivered dose of hemodialysis and peritoneal dialysis have now been developed. These methods permit an objective evaluation of the relationship between the delivered dose of dialysis and patient morbidity and mortality. These methods suggest that the dose of hemodialysis and peritoneal dialysis has been suboptimal for many patients in the United States.

- Factors contributing to underdialysis of some patients include problems with vascular and peritoneal access, nonadherence to the dialysis prescription, and underprescription of the dialysis dose.
- Until prospective, randomized, controlled trials have been completed, a delivered hemodialysis dose at least equal to a measured $K_{dr} t/V$ of 1.2 (single pool) and a delivered peritoneal dialysis dose at least equal to a measured $K_{pr} t/V$ of 1.7 (weekly) are recommended.
- Cardiovascular mortality accounts for approximately 50 percent of deaths in dialysis patients. Relevant risk factors should be treated as soon as possible after diagnosis of chronic renal failure. These factors include hypertension, smoking, and chronic anemia.
- Patients with diabetes mellitus face especially severe cardiovascular risk, which contributes to reduced survival on dialysis.
- Malnutrition is another important co-morbid condition contributing to mortality. A serum albumin of less than 3.5 g/dL is clearly associated with increased relative risk. Early detection and treatment of malnutrition should substantially improve survival.
- Control of renal osteodystrophy requires patient adherence to the prescribed regimen and careful attention by the renal team to calcium and phosphorus intake and to the use of phosphate binders and calcitriol.
- Early creation of an A-V fistula is preferable to placement of a synthetic graft for vascular access. Both require an experienced, meticulous surgeon.
- Skilled management by nursing and other clinical personnel will help prolong the life of the vascular access.
- Attention to catheter design, placement, and care, and to exchange procedures can minimize infection in patients on peritoneal dialysis.
- Biocompatible dialysis membranes may reduce infection and amyloid deposition in hemodialysis patients, but evidence is inconclusive at present.

- Financial support to conduct clinical investigation, including outcomes and health services delivery research, should be incorporated into the budgets of the Medicare End-Stage Renal Disease program, Health Care Financing Administration, Agency for Health Care Policy and Research, and the Food and Drug Administration. This support will enable the conduct of studies that promise to improve morbidity and mortality, enhance cost-effective care, and create long-term financial savings in the Medicare ESRD program.

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