National Kidney Foundation™

2006 Updates Clinical Practice Guidelines and Recommendations

- Hemodialysis Adequacy
- Peritoneal Dialysis Adequacy
- Vascular Access

Full Text of Guidelines and Recommendations

KDOQI Disclaimer

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Variations in practice will inevitably and appropriately occur when clinicians take into account the needs of individual patients, available resources, and limitations unique to an institution or type of practice. Every health-care professional making use of these CPGs and CPRs is responsible for evaluating the appropriateness of applying them in the setting of any particular clinical situation. The recommendations for research contained within this document are general and do not imply a specific protocol.

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CLINICAL PRACTICE GUIDELINES FOR PERITONEAL DIALYSIS ADEQUACY, UPDATE 2006

CLINICAL PRACTICE GUIDELINES FOR VASCULAR ACCESS, UPDATE 2006

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HEMODIALYSIS ADEQUACY

Hemodialysis Adequacy 2006

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Hemodialysis Adequacy Tables

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Hemodialysis Adequacy Acronyms and Abbreviations

β	Standardized coefficient
β2M	β_2-microglobulin
AAMI	Association for the Advancement of Medical Instrumentation
ACE	Angiotensin-converting enzyme
ADMA	Asymmetric dimethylarginine
AR	Access recirculation
ARB	Angiotensin receptor blocker
AV	Arteriovenous
BMI	Body mass index
BSA	Body surface area
BUN	Blood urea nitrogen
BW	Body weight
C	Concentration
C_0/C	Predialysis to postdialysis concentration ratio
CANUSA	Canada-USA Study
CAPD	Continuous ambulatory peritoneal dialysis
CAPR	Cardiopulmonary recirculation
C_{av}	Average concentration
CFU	Colony-forming unit
CI	Confidence interval
CKD	Chronic kidney disease
CMS	Centers for Medicare and Medicaid Services
COX-2	Cyclooxygenase-2
CPG	Clinical Practice Guideline
CPR	Clinical Practice Recommendation
CQI	Continuous quality improvement
CVD	Cardiovascular disease
DOPPS	Dialysis Outcomes and Practice Patterns Study
DOQI	Dialysis Outcomes Quality Initiative
eKt/V	Urea-equilibrated Kt/V
ECF	Extracellular fluid
ECV	Extracellular volume
EKR	Equivalent renal clearance
G	Urea generation rate
GFR	Glomerular filtration rate
HbA_{1c}	Hemoglobin A_{1c}
HD	Hemodialysis
HEMO Study	Kidney Disease Clinical Studies Initiative Hemodialysis Study

HMG	3-Hydroxy-3-methylglutaryl
HR	Hazard ratio
HRQOL	Health-related quality of life
IDEAL	Initiating Dialysis Early And Late
JNC	Joint National Committee
K_{ce}	Continuous equivalent clearance
K_d	Dialyzer clearance
KDOQI	Kidney Disease Outcomes Quality Initiative
KDQOL-SF™	Kidney Disease and Quality of Life Short Form
K_{ecn}	Dialyzer clearance estimated by conductivity
KLS	Kidney Learning System
K_0A	Dialyzer mass transfer area coefficient
K_r	Residual native kidney urea clearance
KRT	Kidney replacement therapy
Kt/V	Clearance expressed as a fraction of urea or body water volume
Kt/V_{urea}	Urea clearance expressed as Kt/V
Kuf	Ultrafiltration coefficient
K_{urea}	Effective (delivered) dialyzer urea clearance
LVH	Left ventricular hypertrophy
MDRD	Modification of Diet in Renal Disease
NCDS	National Cooperative Dialysis Study
nd	No data reported
nEKR	Equivalent renal clearance normalized to body size
NIH	National Institutes of Health
NIVM	Noninvasive monitoring
NKF	National Kidney Foundation
nPCR	Normalized protein catabolic rate
nPNA	Normalized protein nitrogen appearance rate
NS	Not significant
OR	Odds ratio
PD	Peritoneal dialysis
p38MAPK	p38 mitogen-activated protein kinase
QOL	Quality of life
rKt/V	Residual Kt/V
RC	Remote compartment
RCT	Randomized controlled trial
RKF	Residual kidney function
RR	Relative risk
SD	Standard deviation
spKt/V	Single-pool delivered Kt/V (by dialysis only, exclusive of RKF)
stdKt/V	Standard Kt/V
SRI	Solute removal index
t	Treatment time

t_d	Time from beginning to end of dialysis
TAC	Time-averaged concentration
TCV	Total cell volume
TMP	Transmembrane pressure
UFR	Ultrafiltration rate
URR	Urea reduction ratio
USRDS	United States Renal Data System
V	Volume, usually of body urea distribution or total body water
V_{urea}	Patient's volume of urea distribution

Foreword

The publication of the second update of the Clinical Practice Guidelines (CPGs) and Clinical Practice Recommendations (CPRs) for Hemodialysis represents the second update of these guidelines since the first guideline on this topic was published in 1997. The first set of guidelines established the importance of measuring the dose of dialysis in all long-term dialysis patients and the benefits of placing an arteriovenous fistula in a timely manner to reduce the complications that can occur from using either a gortex graft or a permanent catheter for long-term hemodialysis access. Several of these guidelines have been selected as clinical performance measures by regulatory agencies to drive the process of quality improvement in long-term dialysis patients.

A number of important randomized clinical trials have been performed in long-term hemodialysis patients since the publication of the first set of guidelines. The Kidney Disease Clinical Studies Initiative Hemodialysis (HEMO) Study, a National Institutes of Health (NIH)-sponsored randomized clinical trial of dialysis dose and flux, is the largest study to date performed in long-term hemodialysis patients. Results of these and other studies of long-term hemodialysis patients have been included in the literature review for this updated set of guidelines. In addition, this update includes new guidelines on the preservation of residual kidney function, the management of volume status and blood pressure, and the importance of patient education on all dialysis modalities.

This document has been divided into 3 major areas. The first section consists of guideline statements that are evidence based. The second section is a new section that consists of opinion-based statements that we are calling "clinical practice recommendations" or CPRs. These CPRs are opinion based and are based on the expert consensus of the Work Group members. It is the intention of the Work Group that the guideline statements in Section I can be considered for clinical performance measures because of the evidence that supports them. Conversely, because the CPRs are opinion based, and not evidence based, they should not be considered to have sufficient evidence to support the development of clinical performance measures. The third section consists of research recommendations for these guidelines and CPRs. We have decided to combine all research recommendations for the guidelines into 1 major section and also have ranked these recommendations into 3 categories: critical importance, high importance, and moderate importance. Our intended effect of this change in how the research recommendations are presented is to provide a guidepost for funding agencies and investigators to target research efforts in areas that will provide important information to benefit patient outcomes.

This final version of the Clinical Practice Guidelines and Recommendations for Hemodialysis has undergone extensive revision in response to comments during the public review. Whereas considerable effort has gone into their preparation during the past 2 years and every attention has been paid to their detail and scientific rigor, no set of guidelines and clinical practice recommendations, no matter how well developed, achieves its

purpose unless it is implemented and translated into clinical practice. Implementation is an integral component of the KDOQI process and accounts for the success of its past guidelines. The Kidney Learning System (KLS) component of the National Kidney Foundation is developing implementation tools that will be essential to the success of these guidelines.

In a voluntary and multidisciplinary undertaking of this magnitude, many individuals make contributions to the final product now in your hands. It is impossible to acknowledge them individually here, but to each and every one of them, we extend our sincerest appreciation. This limitation notwithstanding, a special debt of gratitude is due to the members of the Work Group and their co-chairs, John Daugirdas of The University of Illinois at Chicago and Tom Depner at the University of California at Davis. It is their commitment and dedication to the KDOQI process that has made this document possible.

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INTRODUCTION

Nephrologists in the United States in general are savvy physicians who respond quickly to public information about care of their patients. Even before the Kidney Disease Clinical Studies Initiative Hemodialysis (HEMO) Study was concluded, average dialysis doses were increasing in the United States, perhaps stimulated by the study itself, which was widely publicized to promote enrollment among the 72 participating clinics.[1,2] The original National Kidney Foundation (NKF)-Dialysis Outcomes Quality Initiative (DOQI) guidelines for hemodialysis (HD) in 1997 probably also fueled the dose increase. At the time the study was completed, the average single-pool fractional urea clearance Kt/V (spKt/V) in the United States was 1.52 per dialysis given 3 times per week.[3] This was and continues to be significantly greater than the minimum of 1.2 established originally in 1994 by a consortium of nephrologists.[4,5] The original minimum recommended dose was based mostly on opinions generated from observational studies and was reiterated by the Kidney Disease Outcomes Quality Initiative (KDOQI) in 2001.[6]

The HEMO Study showed that the minimum dose established by the previous KDOQI guidelines is appropriate when dialysis is performed 3 times per week for 2.5 to 4.5 hours.[1] Dialysis providers no longer need to focus on providing more dialysis by using bigger dialyzers and higher flow rates, but they cannot sit back and relax because the yearly mortality rate for patients with chronic kidney disease (CKD) stage 5 remains unacceptably high in the United States (>20% per year in 2002, and 17% per year in the HEMO Study). This ongoing high mortality rate has served as an incentive for investigators seeking better alternative solutions for dialysis-dependent patients and has spurred interest in alternative therapies and modes of therapy, such as hemofiltration, daily dialysis, sorbent therapy, better volume control, use of ultrapure water, and other interventions. Mortality differences among countries are now explained partially by differences in patient selection and comorbidity, but a considerable gap remains, especially when statistics in the United States are compared with those in Japan, where annual mortality rates are less than 10%. The Dialysis Outcomes and Practice Patterns Study (DOPPS) analyses show that these differences are not caused by different methods for gathering statistics.[7] The HEMO Study showed that the differences are not caused by higher doses in Japan.[1] Better survival in the Japanese may be caused by genetic differences that enhance survival of Asian dialysis patients, whether treated in the United States or Japan.[8,9] Some consolation can be gained from the most recent data published by the United States Renal Data System (USRDS) and Centers for Medicare & Medicaid Services (CMS) that show a reduction in mortality rates during the past 2 decades.[10]

The HEMO Study broadened the scope of interest and opened the eyes of the dialysis health care industry to the issue of dialysis adequacy. It did not settle the question of small-solute toxicity, but it served to redirect attention to other possible causes of morbidity, mortality, and poor quality of life (QOL). These include retention of solutes that are poorly removed by diffusion or convection because of their large size or binding to serum proteins, solute sequestration, physiological stress caused by either the dialysis itself or the intermittent schedule of dialyses that causes fluctuations in fluid balance and solute concentrations, or accumulation of such non–uremia-associated toxins as drug

metabolites that are known to accumulate in dialyzed patients. In the latter case, reducing or stopping antihypertensive drug therapy may have hidden benefits. The caregiver can be a source of the problem, as evidenced by past experience with aluminum toxicity.

The enormous risk for cardiovascular disease (CVD) in patients with CKD stage 5 compared with patients with normal renal function suggests a toxic phenomenon. Perhaps alternate pathways for toxin removal are damaged in patients with CKD, causing accumulation of toxins not normally eliminated by the kidneys. Other possible explanations for the high risk for CVD and cerebrovascular disease include a yet to be discovered renal effect that may protect the vascular endothelium. This role of kidney disease in patients with heart failure and the "cardiorenal syndrome" may be related to cardiovascular risks in patients with renal disease.[11] It is worth noting that the loss of hormones normally produced by the kidney is a well-established cause of disability and mortality that is not responsive to dialysis. The strong association of survival with residual native kidney function in both HD and peritoneal dialysis (PD) patients is consistent with such an effect.

The potential for inflammation caused by contaminated dialysate or soft-tissue reactions to calcium deposits may contribute to the observed strong relationship among inflammatory markers, CVD, and renal disease. It is possible that the high morbidity and mortality rates are not related to dialysis at all. If so, more attention should be given to comorbidity and QOL and less attention to the adequacy of dialysis. At this juncture in the search for answers and solutions, both imagination and science are needed.

New issues addressed in these updated guidelines include the timeline for initiation of dialysis therapy, which also is addressed by the PD and Vascular Access Work Groups. Emphasis was placed on patients destined for HD therapy, but efforts also were made to coordinate these guidelines with the initiation guidelines generated by the other work groups that recommended stepped increases in the prescribed dialysis dose, early referral, and early access placement.

Predialysis blood urea nitrogen (BUN) is easy to measure, but the postdialysis concentration is a moving target. Its decrease during dialysis is sharply reversed when the treatment ceases; thus, timing of the postdialysis blood sample is critical. The Work Group determined that markedly slowing blood flow at the end of dialysis before sampling the blood is the safest and simplest technique for achieving the uniformity needed for reliable and reproducible values of Kt/V.

The delivered Kt/V determined by single-pool urea kinetic modeling continues to be preferred as the most precise and accurate measure of dialysis. Simplified formulas are acceptable within limits, and urea reduction ratio (URR) continues to be viable, but with pitfalls. Conductivity (ionic) clearance also is accepted, but tends to underestimate dialyzer urea clearance. The Work Group believed that more attention should be given to residual kidney function (RKF) in light of recent evidence linking outcomes more closely to RKF than to dialysis dose. Although we do not recognize a state of "overdialysis," patient QOL is compromised by dialysis; therefore, giving unnecessary treatment should be avoided, especially now that we recognize a ceiling dose above which morbidity and mortality are not improved. Pitfalls and controversies about methods for adding RKF to

dialyzer clearance were reviewed, but were considered too complex for the average dialysis clinic to manage. Implementation was simplified by setting a cutoff urea clearance of 2 mL/min, above which inclusion of residual native kidney urea clearance (K_r) is recommended and below which it can be ignored. Although the cutoff value is somewhat arbitrary, it serves to separate patients into 2 groups: 1 group in which the trouble and expense of measuring RKF can be avoided, and the other group in which more attention should be focused on RKF to potentially improve QOL. In the latter group are patients for whom recovery of renal function may be anticipated. Patients in the group with RKF greater than 2 mL/min (~10% to 30%) should have regular measurements of native kidney clearance to avoid underdialysis as function is lost and to avoid prolonging dialysis if function recovers. Twice-weekly dialysis may be permissible in a few patients within the group with RKF greater than 2 mL/min who have stable function and do not have excessive fluid gains. Because RKF is preserved better in current HD patients compared with the past, a separate guideline was established to encourage preservation of RKF.

More frequent dialysis is becoming more common; thus, methods for measuring the dose are required. Partially controlled studies suggest that QOL improves, hypertension is alleviated, left ventricular hypertrophy (LVH) regresses, and sleep disturbances abate with daily or nocturnal HD. The Work Group reviewed current methods and gave practice recommendations for measuring the dose in these patients. More definitive recommendations may come from the National Institutes of Health (NIH) Frequent HD Network Study that currently is enrolling patients.

The Work Group focused more intently on the target dose and its relationship with the minimum dose which, in light of HEMO Study findings, remains 1.2 Kt/V units per dialysis for patients dialyzed 3 times per week. Data from the HEMO Study also revealed a coefficient of variation within patients of approximately 0.1 Kt/V units; therefore, the previous target of 1.3 was considered too low. To grant 95% confidence that the dose will not decrease to less than 1.2 per dialysis, the target dose was increased to 1.4 per dialysis. This is in keeping with current practice and is consistent with the target spKt/V of approximately 1.4 set by the European Standards Group.[12] The Work Group favored high-flux membranes. The HEMO Study did not provide definitive answers, but data suggested that dialysis vintage and flux are related and CVD might be affected favorably by the use of high-flux dialysis.[1] The issue of sex also was addressed by the Work Group, which believed that dialysis doses and targets should remain the same in women compared with men. However, in light of suggestive findings from the HEMO Study and observational studies, clinicians should be aware of a possible increased responsiveness to dialysis in females compared with males.[13]

Concern was raised by the Work Group about malnourished patients with respect to both the initiation and adequacy of HD. Initiation is confounded by errors in calculation of glomerular filtration rate (GFR) for patients with diminishing muscle mass, and adequacy is confounded by the effect of malnutrition on patients' water volume (V), the denominator of the integrated urea clearance expression (Kt/V). Estimation equations for calculating GFR before starting dialysis therapy are based on serum creatinine level, but are adjusted for sex, size, race, and other factors that tend to alter the relationship

between concentration and clearance. Most of these factors either increase or decrease the generation of creatinine, but the patient's state of nutrition—which is well known to affect creatinine generation—is not a variable in this equation. The consequent error in malnourished patients would tend to underestimate GFR and thus endanger the patient from the ill consequences of the delayed initiation of dialysis therapy. In addition, if the patient is malnourished, dialysis probably is better started early.

After a patient starts dialysis therapy, loss of weight because of malnutrition will decrease V, increasing the Kt/V, potentially to values higher than the desired target range. Reducing the dialysis dose (Kt/V) in such patients may lead to potential harm from inadequate dialysis. The Work Group addressed this problem in Clinical Practice Recommendation (CPR) 4.6, which calls for an increase in Kt/V when signs of malnutrition are present. The magnitude of the increase is left to the clinician, who might take into consideration the absolute level of Kt/V and cause of the malnutrition. If Kt/V is already much greater than the minimum, an additional increase probably would not benefit the patient. Similarly, if malnutrition is caused by a condition other than uremia, increasing the dose may have no effect. This issue will require revisiting in the future, hopefully with more available hard data.

The importance of missed dialysis treatments was emphasized repeatedly by the Work Group. Although difficult to quantify in terms of a guideline, patient cooperation and compliance is a major determinant of survival.[14–16] To ensure compliance, efforts should be made to maintain the patient's confidence in the health care system at all levels. However, patient satisfaction in general and patient encounters with physicians have not shown a strong correlation with survival.[17]

Other aspects of dialysis adequacy were addressed, including fluid balance, blood pressure control, and membrane biocompatibility. Reuse has moved to the background among issues of concern in dialysis clinics for 2 reasons: (1) many clinics in the United States no longer reuse dialyzers, and (2) risks associated with reuse were examined and found to be very small. Monitoring outcome goals within each dialysis clinic is vitally important for quality assurance and quality improvement, and this issue been added as a Clinical Practice Guideline (CPG) for HD and PD adequacy. This outcomes-monitoring guideline is not intended to guide individual patient care, but is intended for the dialysis clinic as a whole.

More data are available regarding adequacy in pediatric HD patients, but the numbers thankfully remain small, so definitive evidence is lacking. The greater metabolic rate per unit of surface area in children has been invoked by some to justify a higher dose. Use of V as a denominator (see previous discussion of V) also may endanger smaller patients. In other respects, for younger smaller patients, we have little evidence to support a different dosing regimen than that delivered to adults.

Since the last issuance of the KDOQI Guidelines, the Standards Group of the European Renal Association in 2002 published adequacy guidelines for HD measurement, dosing, and minimum standards.[12] The HD adequacy group chose urea-equilibrated Kt/V (eKt/V), recommending the Daugirdas method[69] for converting spKt/V to eKt/V, with a target of 1.2 per dialysis (spKt/V $\sim$ 1.4). The target was higher than that previously recommended

by KDOQI (spKt/V = 1.3 per dialysis), but the rationale for increasing the target was not clearly delineated. The group recommended using the mean of creatinine and urea clearance as a measure of RKF and discouraged twice-weekly dialysis.

In the United States, we have come a long way, from marveling about how HD can snatch patients from the jaws of death and keep them alive indefinitely to coping with 0.1% of the population depending on HD for life support. Nephrologists have learned that, although numbering more than 300,000, these patients represent a small segment of approximately 20 million people in the United States with kidney disease who have survived tremendous risks for CVD and other morbid diseases to develop CKD stage 5. They often arrive in the dialysis clinic with a legacy of diabetes, CVD, and inflammatory diseases that continue to progress. The challenge for today's health care workers and the dialysis industry is to provide an opportunity for these patients to live long and comfortably with freedom to pursue their dreams, even if for only a relatively short length of time in those at high risk. We need to be all things for these patients, but first and foremost, we must deliver the best dialysis therapy we can with available technology. These new KDOQI HD CPGs, CPRs, and Research Recommendations are designed to provide a clearer pathway and help everyone move in that direction.

I. Clinical Practice Guidelines for Hemodialysis Adequacy

GUIDELINE 1. INITIATION OF DIALYSIS

1.1 Preparation for kidney failure:
Patients who reach CKD stage 4 (estimated GFR < 30 mL/min/1.73 m^2) should receive timely education about kidney failure and options for its treatment, including kidney transplantation, PD, HD in the home or in-center, and conservative treatment. Patients' family members and caregivers also should be educated about treatment choices for kidney failure. (B)

1.2 Estimation of kidney function:
Estimation of GFR should guide decision making regarding dialysis therapy initiation. GFR should be estimated by using a validated estimating equation (Table 1) or by measurement of creatinine and urea clearances, not simply by measurement of serum creatinine and urea nitrogen. Table 2 and Table 3 summarize special circumstances in which GFR estimates should be interpreted with particular care. (B)

1.3 Timing of therapy:
When patients reach stage 5 CKD (estimated GFR < 15 mL/min/1.73 m^2), nephrologists should evaluate the benefits, risks, and disadvantages of beginning kidney replacement therapy. Particular clinical considerations and certain characteristic complications of kidney failure may prompt initiation of therapy before stage 5. (B)

BACKGROUND

Optimum timing of treatment for patients with CKD prevents serious and uremic complications, including malnutrition, fluid overload, bleeding, serositis, depression, cognitive impairment, peripheral neuropathy, infertility, and increased susceptibility to infection. However, all forms of kidney replacement therapy entail important trade-offs. As GFR decreases, patients and physicians must weigh many risks and benefits. Decision making is more complex for older and more fragile patients. Together, patients and physicians must continually reconsider whether the anticipated physiological benefits of solute clearance and extracellular fluid (ECF) volume control now outweigh the physical risks and psychosocial toll of therapy. In some cases, social and psychological factors may lead to earlier dialysis therapy initiation, and in some cases, to later initiation. The initiation of dialysis therapy remains a decision informed by clinical art, as well as by science and the constraints of regulation and reimbursement.

For some patients, conservative therapy, without dialysis or transplantation, is the appropriate option.[27–29] If the patient makes this choice, the health care team should strive to maximize QOL and length of life by using dietary and pharmacological therapy to minimize uremic symptoms and maintain volume homeostasis. These include, but are not limited to, use of low-protein diets, ketoanalogs of essential amino acids, loop diuretics,

Table 1. Validated GFR-Estimating Equations

Age ≥18 Years
Cockcroft-Gault Equation [18]
MDRD 4 Variable Equation [20]
MDRD 6 Variable Equation [19]
Age <18 Years
Schwartz Formula [21]

MDRD: Modification of diet in renal disease

and sodium polystyrene sulfonate. Nephrologists also should be familiar with the principles of palliative care[30] and should not neglect hospice referral for patients with advanced kidney failure.

RATIONALE

Preparation for Kidney Failure (CPG 1.1)

Timely Education in Stage 4 CKD. Timely patient education as CKD advances can both improve outcomes and reduce cost.[31] Planning for dialysis therapy allows for the initiation of dialysis therapy at the appropriate time and with a permanent access in place at the start of dialysis therapy. Planning for kidney failure should begin when patients reach CKD stage 4 for several reasons. The rate of progression of kidney disease may not be predictable. There is substantial variability in the level of kidney function at which uremic symptoms or other indications for dialysis appear. Patients vary in their ability to assimilate and act on information about kidney failure. Local health care systems vary in the delays associated with patient education and scheduling of consultations, tests, and procedures. Results of access creation procedures vary, and the success or failure of a procedure may not be certain for weeks or months. Timely education will: (1) allow patients and families time to assimilate the information and weigh treatment options, (2) allow evaluation of recipients and donors for preemptive kidney transplantation, (3) allow staff time to train patients who choose home dialysis, (4) ensure that uremic cognitive impairment does not cloud the decision, and (5) maximize the probability of orderly and planned treatment initiation using the permanent access.

Predialysis education to inform the patient and support persons about the relative value of various renal replacement modalities offers a freedom of choice that must be honored. Education and choice of modality also are vital to the timely placement of vascular or peritoneal access, training for home dialysis, and actual timing of the initiation of the selected first modality. A comprehensive preemptive discussion of these issues will enable patients and their support groups to make rational decisions and will serve to involve patients as active participants in their personal health care. Playing an active role in one's own health care, although thwarting the natural defense mechanism of denial, reduces risks from negligence and psychological depression that have been associated with poor outcomes after dialysis therapy is started.[32]

Contingency Plans. Optimal timing of vascular access creation may depend on plans regarding transplantation and/or PD treatment. Early attempts at native vein arteriovenous (AV) fistula creation are particularly important in patients who are: (1) not transplant candidates or (2) lack potential living kidney donors and also seem unlikely to perform PD. For patients hoping to undergo "preemptive" transplantation, thus avoiding dialysis treatment, the decision about whether to attempt AV fistula creation at CKD stage 4 (and, if so, when in stage 4) depends on the nephrologist's estimate of the likelihood that preemptive transplantation will be accomplished. For patients interested in performing PD, the decision about whether to attempt AV fistula creation at CKD stage 4 depends on the nephrologist's estimate of the probability that PD will be successful. The benefits of planning for kidney failure treatment are reflected in the literature comparing the consequences of early and late referral of patients with CKD to nephrologists.[33–36]

Education of Health Care Providers and Family Members. Optimally, education in preparation for kidney failure will include not only the patient, but also other individuals who are likely to influence his or her decisions. These may include family, close friends, and primary care providers. Their understanding of such issues as the impact of interventions designed to slow progression, the absence of symptoms despite underlying kidney disease, transplantation eligibility, the choice between PD and HD, and the choice and timing of vascular access may have critical consequences for the patient.

Estimation of Kidney Function (CPG 1.2)

Use of GFR-Estimating Equations and Clearances Rather Than Serum Creatinine to Guide Dialysis Initiation. Variability in creatinine generation across the population makes serum creatinine level alone an inaccurate test for patients with kidney failure likely to benefit from dialysis treatment. For most patients in CKD stages 4 and 5, estimating equations based on values of serum creatinine and other variables approximate GFR with adequate accuracy. For most patients, measured clearance does not offer a more accurate estimate of GFR than prediction equations.[37]

Variation in Creatinine Generation. It is well established that creatinine generation may be unusually low in patients with a number of conditions and may be increased in individuals of unusually muscular habitus (Table 2). In these situations, GFR estimated by using creatinine and urea clearances may be substantially more accurate (compared with radionuclide GFR) than results of creatinine-based estimating equations. In patients

Table 2. Causes of Unusually Low or High Endogenous Creatinine Generation

Condition	Creatinine Generation
Vegetarian diet [22]	Low
Muscle wasting [22]	Low
Amputation [22]	Low
Spinal cord injury [23]	Low
Advanced liver disease [24,25]	Low
Muscular habitus [22]	High
Asian race [26]	Low

Table 3. Causes of Unusually Low or High Kidney Tubular Creatinine Secretion

Drug or Condition	Kidney Tubular Creatinine Secretion
Trimethoprim [22]	Low
Cimetidine [22]	Low
Fibrates (except gemfibrozil) [22]	Low
Advanced liver disease [25]	High

for whom endogenous creatinine generation is likely to be unusually low or high, GFR should be estimated by using methods independent of creatinine generation, such as measurement of creatinine and urea clearances.

Variation in Tubular Creatinine Secretion. Several drugs are known to compete with creatinine for tubular secretion, and advanced liver disease has been associated with increased tubular creatinine secretion (Table 3). Decreased secretion will result in artifactually low GFR estimates, and increased secretion will result in overestimation of GFR by means of estimating equations. In patients for whom tubular creatinine secretion is likely to be unusually low or high, the consequent bias to all creatinine-based measures should be considered in interpreting GFR estimates.

Timing of Therapy (CPG 1.3)

Initiation of Kidney Replacement Therapy. This guideline is based on the assumption that overall kidney function correlates with GFR. Because the kidney has many functions, it is possible that 1 or more functions will decrease out of proportion to the decrease in GFR. Therefore, caregivers should be alert to signs of declining health that might be directly or indirectly attributable to loss of kidney function and initiate kidney replacement therapy (KRT) earlier in such patients. However, they should consider that dialysis therapy is not innocuous and does not replace all functions of the kidney and that HD-related hypotension may accelerate the loss of RKF. This may particularly be true of HD.

Individual factors—such as dialysis accessibility, transplantation option, PD eligibility, home dialysis eligibility, vascular access, age, declining health, fluid balance, and compliance with diet and medications—often influence the decision about the timing of when to start dialysis therapy. It may be optimal to perform kidney transplantation or begin home dialysis before patients reach CKD stage 5. Even when GFR is greater than 15 mL/min/1.73 m^2, patients may have a milder version of uremia that may affect nutrition, acid-base and bone metabolism, calcium-phosphorus balance, and potassium, sodium, and volume homeostasis. Conversely, maintenance dialysis imposes a significant burden on the patient, family, society, and health system. This is complicated further by the potential risks of dialysis therapy, especially those related to dialysis access and dialysate. These considerations necessitate conservative management until GFR decreases to less than 15 mL/min/1.73 m^2, unless there are specific indications to initiate dialysis therapy. Thus, the recommended timing of dialysis therapy initiation is a compromise designed to maximize patient QOL by extending the dialysis-free period while avoiding complications that will decrease the length and quality of dialysis-assisted life.

Theoretical considerations support initiation of dialysis therapy at a GFR of approximately 10 mL/min/1.73 m^2, and this was the recommendation of the 1997 NKF KDOQI HD Adequacy Guideline.[38–40] In 2003, mean estimated GFR at the initiation of dialysis therapy was 9.8 mL/min/1.73 m^2. This mean value reflects lower average values (~7 to 9 mL/min/1.73 m^2) for young and middle-aged adults and higher average values (~10 to 10.5 mL/min/1.73 m^2) for children and elderly patients. Average GFR at initiation has increased in all age groups since 1995; it has increased most in the oldest patients.[41]

It is difficult to make a recommendation for initiating KRT based solely on a specific level of GFR. Several studies concluded that there is no statistically significant association between renal function at the time of initiation of KRT and subsequent mortality.[42–45] However, others suggested that worse kidney function at initiation of KRT is associated with increased mortality or morbidity.[40–46] When corrections are made for lead-time bias, there is no clear survival advantage to starting dialysis therapy earlier in comparative outcome studies of patients initiating dialysis therapy at higher versus lower GFRs.[47,48]

Furthermore, it now is clear from observational registry data from the United States, Canada, and the United Kingdom[48A] that patients with comorbidities initiate dialysis therapy at higher levels of estimated GFR.[41,49,50] It is reasonable to assume that this practice is based on experience and the speculation, hope, and/or impression that dialysis therapy may alleviate or attenuate symptoms attributed to the combination of the comorbidity plus CKD. Because symptoms of early uremia are fairly nonspecific, one can expect that patients with symptoms associated with their comorbidities would initiate dialysis therapy early. Healthy and hardy patients with less comorbidity likely will develop symptoms at a later stage than a frailer, early-starting comparative group. Frail patients who start dialysis therapy earlier do not live as long as hardy patients who start dialysis later. However, this remains merely an interpretation of observational data. A more definitive answer may emerge from properly designed prospective trials. One such trial expects to report in 2008. The Initiating Dialysis Early and Late (IDEAL) Study from New Zealand and Australia is a prospective, multicenter, randomized, controlled trial (RCT) to compare a broad range of outcomes in patients starting dialysis therapy with a Cockcroft-Gault GFR of 10 to 14 versus 5 to 7 mL/min/1.73 m^2.[51]

In 2000, the NKF KDOQI CPG on Nutrition in CKD advocated that—in patients with CKD and estimated GFR less than 15 mL/min/1.73 m^2 who are not undergoing maintenance dialysis—if: (1) protein-energy malnutrition develops or persists despite vigorous attempts to optimize protein-energy intake, and (2) there is no apparent cause for it other than low nutrient intake, initiation of KRT should be recommended.[52] Furthermore, those guidelines set forth measures for monitoring nutritional status and identifying its deterioration. Those guidelines are consistent with the present recommendations.

LIMITATIONS

Individuals vary tremendously in the physiological response to uremia and dialysis treatment. Patients expected to experience uremic complications often survive much longer than the physician anticipates, without apparent adverse consequences. Patients also vary in their willingness and ability to adhere to a medical regimen intended to forestall

the need for dialysis treatment. Health care systems and providers vary greatly in their capability to monitor patients with advanced kidney failure safely without dialysis treatment. At best, the decision to initiate dialysis treatment or perform preemptive transplantation represents a joint decision by patient and physician, reflecting their mutual understanding of the compromises and uncertainties. It requires clinical judgment based on clinical experience.

GUIDELINE 2. METHODS FOR MEASURING AND EXPRESSING THE HEMODIALYSIS DOSE

Quantifying HD is the first step toward assessment of its adequacy. Fortunately, the intermittent rapid decrease in urea concentration during HD allows a relatively easy measurement of the dose.

2.1 The delivered dose of HD should be measured at regular intervals no less than monthly. (A)

2.2 The frequency of treatments should be included in the expression of dose. (A)

2.3 The dose of HD should be expressed as $(K_{urea} \times T_d)/V_{urea}$ (abbreviated as Kt/V), where K_{urea} is the effective (delivered) dialyzer urea clearance in milliliters per minute integrated over the entire dialysis, T_d is the time in minutes measured from beginning to end of dialysis, and V_{urea} is the patient's volume of urea distribution in milliliters. (B)

2.4 The preferred method for measurement of the delivered dose is formal urea kinetic modeling. Other methods may be used provided they give similar results and do not significantly overestimate the modeled dose. (A)

2.5 Methods described in Appendix can be used to add the continuous component of residual urea clearance to the intermittent dialysis spKt/V to compute an adjusted intermittent Kt/V. Laboratories reporting adjusted session Kt/V values should clearly identify such measurements by a different name (eg, "adjusted" Kt/V or "total" Kt/V). (B)

BACKGROUND

HD is a process that removes accumulated solute from a patient who has total or near-total loss of kidney function. The process is diffusion of solute from the blood into a physiological salt solution (dialysate) that is separated from the blood by a thin semipermeable membrane, the major component of the dialyzer. The rate of solute diffusion is a vital part of any measurement of dialysis or its adequacy, but the rate of diffusion across the dialyzer membrane is driven by blood concentration and is proportional to it (following first-order kinetics). This linear proportionality for simple diffusion (and convection) allows expression of the dialysis effect as a ratio of the diffusional removal rate (eg, mg/mL) to blood concentration (eg, mg/mL). This ratio, defined as "clearance," is a fundamental measure of dialysis that tends to remain constant during intermittent treatments as both blood concentrations of small solutes and solute removal rates decrease. Clearance can be measured instantaneously by sampling blood on both sides of the dialyzer or, more appropriately for clinical applications, as an average measurement during the entire duration of a single dialysis treatment by sampling blood at the beginning and end of treatment. This latter approach is simpler and gives a measure of the true delivered dose of HD.

RATIONALE

Frequency of Measurements (CPG 2.1)

Numerous outcome studies have shown a correlation between delivered dose of HD and patient mortality and morbidity (see Table 8, Guideline 4).[14,53–58] To ensure that patients with CKD treated with HD receive adequate treatments, delivered dose of dialysis must be measured. Clinical signs and symptoms alone are not reliable indicators of dialysis adequacy. In studies of the relationship between delivered doses of HD and patient outcomes, the typical frequency of measurement was monthly.[1,54–56,58] Less frequent measurements may compromise the timeliness with which deficiencies in the delivered dose of HD are detected and hence may delay implementation of corrective action. Monthly measurements also are pragmatic because patients undergo blood testing on a monthly basis in nearly all dialysis clinics. Alternatively, the dose can be measured more frequently by using on-line methods (see the discussion of on-line clearance that follows).

Duration and Frequency of HD (CPG 2.2)

Because—as currently applied—therapeutic HD is nearly always delivered intermittently, expression of the dialysis dose as a clearance is advantageous because clearance is relatively constant throughout the treatment despite a marked decrease in blood concentrations of easily dialyzed solutes. To account for variations in the duration and schedule of treatments, dose expression must include factors for both duration and frequency. This contrasts with measurements of continuous kidney function and continuous (peritoneal) dialysis for which a simple clearance rate suffices. To account for the variable time each patient spends on dialysis (treatment time or "t"), the clearance rate can be expressed per dialysis instead of per unit of time. Expression of the dose as a volume processed per dialysis instead of volume flow (volume per unit of time) eliminates the need to measure "t" when calculating the dose (see calculation of clearance next). To account for differences in frequency, either the number of treatments per week must be appended to the expression of dose (eg, 3 treatments per week) or the dose can be expressed as a function of repeating intervals (eg, per week instead of per dialysis). To compare doses among treatments given at different frequencies, the dose for a single treatment typically is multiplied by the number of treatments per week. For example, a target dose of 1.3 urea volumes per dialysis would equate to a target of 3.9 volumes per week for patients treated 3 times per week. Because a more frequent schedule also is more efficient, additional adjustments are required for frequency. The Work Group believed that doses expressed per dialysis should include an element for the number of treatments per week (eg, spKt/V[3] for 3 treatments per week). A more detailed discussion of these effects can be found under "Effects of Dialysis Frequency" in CPR 4, *Minimally Adequate Hemodialysis.*

Value of Urea as a Marker of Dialyzer Clearance (CPG 2.3)

While the ultimate goal of dialysis treatments is a decrease in solute levels in the patient, measurement of isolated solute levels can be misleading if the solute measured is not representative of all uremic toxins. Because no solute probably qualifies in this respect, it is reasonable to pick as a marker an easily dialyzed solute, such as urea, for which

concentrations in the patient decrease significantly during the treatment. Urea clearance determined from a ratio of concentrations, rather than from an absolute value, is a sensitive marker of small-solute diffusion across the dialyzer. Because dialysis most effectively removes small solutes, urea Kt/V is a sensitive measure of the overall dialysis dose.

The Denominator Is the Patient's Water Volume (CPG 2.3)

Native kidney clearance traditionally is adjusted to body size and specifically to body surface area (BSA). This adjustment normalizes the clearance effect among larger and smaller individuals and among species of widely differing size.[59,60] However, for intermittent dialysis of solutes that distribute in body water, it is mathematically more convenient to use body water volume as the denominator because by doing so, the clearance expression is reduced from a flow to a fractional removal rate (the rate constant). The product of the rate constant (K/V) and time (t) can be determined easily as a logarithmic function of the predialysis to postdialysis concentration ratio (C_0/C): $Kt/V = \ln(C_0/C)$.[61,62] Kt/V is a measure of clearance per dialysis factored for patient size, measured as V. Expressing clearance in this manner eliminates the need to specifically measure the individual components of Kt/V (clearance, time, and body size). Instead, predialysis and postdialysis solute concentrations (C_0 and C) provide a measure of average clearance per dialysis factored for the patient's size in this simplified setting with no ultrafiltration or urea generation.

Ultrafiltration and Other Components (CPG 2.4)

However, enhancement of clearance caused by ultrafiltration that almost always occurs simultaneously with diffusional clearance during therapeutic dialysis adds a significant component that must be included along with the simultaneous solute generation rate in the Kt/V calculation. The more complex mathematical expressions that incorporate these vital components require computer programs to precisely calculate Kt/V by iterating the following equation[363]:

$$C = C_0\left[\frac{V - B \bullet t}{V}\right]^{\left(\frac{K_r + K_d + B}{B}\right)} + \frac{G}{K_r + K_d + B}\left[1 - \left[\frac{V - B \bullet t}{V}\right]^{\left(\frac{K_r + K_d + B}{B}\right)}\right]$$

where V is postdialysis urea distribution volume, G is urea generation rate, K_r is residual native kidney urea clearance, B is rate of change in V during dialysis, and K_d is dialyzer urea clearance. Despite the complexities of the equation and the iterative computer

model, the expression of clearance simulates solute removal from only a single compartment. Finite diffusion rates among multiple body compartments add complexities that require additional mathematical adjustments, usually requiring numerical analysis for a solution. Fortunately, the errors encountered when applying the simpler model to the usual thrice-weekly dialysis schedule tend to cancel one another, allowing accurate assessment of dose with the single-compartment model.[63,64]

Simpler Methods (CPG 2.4)

The arguments discussed show that the major determinants of Kt/V are the decrease in urea concentration during dialysis, contraction of body water volume during dialysis, and generation of urea during the treatment. Use of these 3 variables in an empirical formula allows an approximation of Kt/V from a single equation, bypassing the need for formal modeling[65]:

$$\frac{K \cdot t}{V} = -\ln(R - 0.008 \cdot t) + (4 - 3.5 \cdot R)\frac{\Delta BW}{BW}$$

where *R* is the ratio of postdialysis BUN to predialysis BUN, *t* is time on dialysis in hours, and *BW* is body weight. Although this and other similar methods give an approximation of the true spKt/V, calculated Kt/V matches the computer-derived modeled Kt/V fairly closely when applied to dialysis given 3 times per week for 2.5 to 5 hours. Disadvantages of this equation when used alone to measure Kt/V include no measure of the net protein catabolic rate (PCR) that urea modeling generates and errors when applied to short, frequent, or prolonged dialysis.[65] However, additional simplified equations that include the absolute value of predialysis BUN can be used to calculate normalized PCR (nPCR), also called normalized protein nitrogen appearance rate (nPNA).[66]

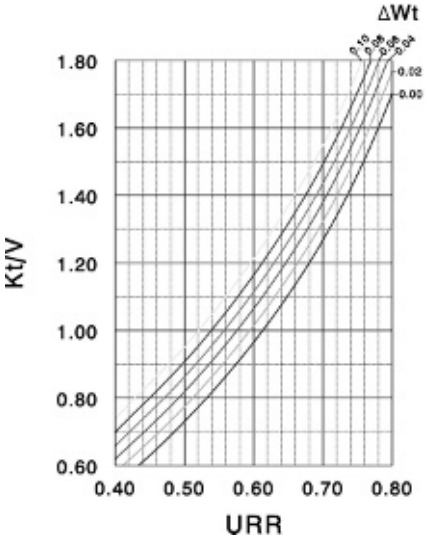
Because the relative decrease in urea concentration during therapeutic dialysis is the most significant determinant of Kt/V, direct measurement of URR has been proposed as a simpler substitute for complex equations or formal urea modeling to calculate dialysis dose.

$$URR = (C_0 - C)/C_0$$

Although URR correlates well with spKt/V in population studies, significant variability in correlation in individual patients occurs because URR fails to include both the contraction in extracellular volume (ECV) and the urea generation that typically occur during routine HD.

Fig 1 shows that for a given value of Kt/V, URR may vary considerably depending on the fraction of weight lost during dialysis. However, when outcomes, including death, are correlated with either URR or Kt/V, no difference in degree of correlation is detectable. The reason for this lack of a better correlation with Kt/V probably results from the narrow range of doses achieved during HD and the curvilinear relationship between the 2 parameters. When level of kidney replacement increases, especially when treatment is given daily, URR approaches zero. URR also is zero in continuously dialyzed patients or patients with normal kidney function. Other disadvantages of URR include the

Figure 1. Impact of ultrafiltration on delivered dose of HD measured by using spKt/V and URR. The curves are derived from formal single-pool modeling of urea kinetics assuming a 3-hour dialysis, no RKF, and a volume of urea distribution that is 58% of BW. ΔWt refers to net ultrafiltration losses as a fraction of final BW. Reprinted with permission.[67]



inability to adjust the prescription accurately when the value is off target (by adjusting K or t), inability to add the effect of RKF, and inability to troubleshoot by comparing prescribed with delivered dose.

Native Kidney Function (CPG 2.5)

The Canada-USA (CANUSA) Study of PD patients suggested that native kidney function contributed more than dialysis function to improve outcomes at each level of total creatinine or urea clearance.[68] In view of the HEMO Study findings that prolonging HD in the current thrice-weekly model does not improve outcome or QOL[1], failure to include residual clearance in calculation of the required dose could lead to "excessive" dialysis that would compromise patient QOL. The reduction in quality years may vary from patient to patient, who consider time spent on dialysis of variable quality. These observations strongly support the notion that native kidney function should be included in any expression of overall kidney function (both native and replacement). However, omission will protect the patient from underdialysis when RKF is lost. For further discussion and practice recommendations, see CPR 2, *Methods for Measuring and Expressing the HD Dose.*

Equilibrated Kt/V (eKt/V)(CPG 2.3)

When the time is shortened and dialysis is intensified, the treatment is less efficient because solute disequilibrium is enhanced and more time is available for solutes to accumulate between treatments. Allowance for solute disequilibrium can be made by adjusting spKt/V for the rebound in urea concentration at the end of dialysis. The resulting eKt/V has a time-

Table 4. Methods for Calculating eKt/V

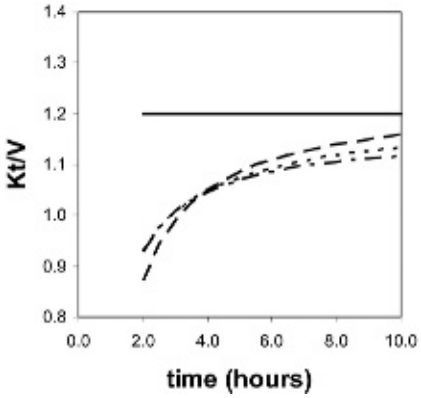
Daugirdas [69]	
AV access[a]	
spKt/V – 0.60spK/V + 0.03	(spK/V is a fraction per hour: spK/V = spKt/V/(hr on dialysis)
spKt/V – 36spK/V + 0.03	(K/V is a fraction per minute: spK/V = spKt/V/(min on dialysis)
spKt/V(1 – 0.60/t) + 0.03	(t in hr)
spKt/V(1 – 36/t) + 0.03	(t in min)
Venous access[a]	
spKt/V - 0.47K/V + 0.02	(K/V is a fraction per hr)
spKt/V – 28spK/V + 0.02	
spKt/V(1 – 0.47/t) + 0.02	
spKt/V(1 – 28/t) + 0.02	
Tattersall [b 70]	
spKt/V(t/(t + 35))	(t in min)

a These are all equivalent equations.
b The Tattersall equation applies only to AV access.

dependent factor that reflects the intensity of dialysis for a given delivered dose (spKt/V), as shown in Table 4. The first formula by Daugirdas shown in Table 4, often called the "rate equation," was derived from regression data that showed a tight fit with values measured by using the rebounded BUN measured 30 or 60 minutes after dialysis.[69] The Tattersall equation was derived from theoretical considerations of disequilibrium and rebound, but the coefficient was derived from fitting to actual data.[70] The Leypoldt equation is a recent addition, also based on empirical fitting of measured data.[71]

Many, including our European colleagues,[12] would like to convert the dose benchmark from spKt/V to eKt/V for HD (for PD, eKt/V and spKt/V are identical). Concern is raised about rapid dialysis in small patients, for whom the difference between spKt/V and eKt/V is larger (Fig 2). After debating this issue in depth, the KDOQI HD Work Group unanimously decided to disallow shortened dialysis for treatments 3 times per week, but to do

Figure 2. eKt/V as a function of dialysis treatment time. The rate equations for eKt/V (lower 3 lines) predict that dialysis efficiency decreases as time is shortened, creating a larger difference between eKt/V and spKt/V. (— spKt/V, – – Daugirdas,[69] ---- Tattersall et al,[70] – - – Leypoldt et al[71])



this explicitly rather than as a modification of Kt/V (see CPG 4). Use of eKt/V as a benchmark does not prohibit ultrashort dialysis provided the clearance can be increased, for example, by increasing blood and dialysate flow rates or increasing dialyzer surface area. For such highly sequestered solutes as phosphate, this would not improve removal and the shortened dialysis time would compromise fluid removal, as noted in CPG 5. For pediatric and small adult patients, the size-associated mortality risk may be related in part to the shortened dialysis time often prescribed for small patients. Previous reports and recent evidence from the DOPPS showing a positive correlation between dialysis treatment time and mortality support the concept that ultrashort dialysis (<3 hours), despite an adequate spKt/V, should be avoided.[72,72A] Of note, eKt/V determined by using all the formulas in Table 4 first requires measurement of spKt/V, and if the prescribed dose requires adjustment, conversion back to spKt/V is required to determine the change in dialyzer K that is required. Equilibrated K cannot be adjusted directly. In the absence of more evidence that would favor the additional effort and target-range adjustment required to substitute eKt/V for spKt/V, the Work Group elected to stay with the currently established standard.

On-line Clearance (CPG 2.4)

The requirement for monthly measurements of HD adequacy is a compromise between cost and the utility of the measurement. The dose can be assessed more frequently by measuring conductivity (or ionic) clearance across the dialyzer membrane. This method does not require consumables or blood sampling and can be used with each dialysis treatment to predict the delivered Kt/V in real time before the treatment is finished.[73–76] The method is based on the assumption that changes in dialysate conductivity are caused by transmembrane movement of small electrolytes, mostly sodium, that behave like urea. A step up in dialysate sodium concentration followed by a step down while measuring conductivity changes in the effluent dialysate tends to eliminate the effect of cardiopulmonary recirculation (CAPR) and provides a sodium clearance that is similar to or only slightly less than the simultaneously measured cross-dialyzer urea clearance.[76] When applied in this fashion, conductivity clearance can be used safely as a substitute for the blood-side urea method for measuring dialysis dose.

To avoid errors from changes in clearance during dialysis, multiple ionic clearance measurements must be performed throughout the treatment. To calculate Kt/V, time on dialysis and V must be determined accurately. The latter is a potential problem if anthropometric formulas are used to estimate V because these formulas are estimates that often differ significantly from the true value. Discrepancies between anthropometric estimates of BSA and apparent need for dialysis have similarly confounded interpretations of creatinine clearance and GFR during CKD stages 1 to 4. Conversely, errors in modeled V do not translate directly to errors in dialysis dose because they are caused most often by errors in estimated K. The dose, which is based on the ratio K/V, which, in turn, is derived mostly from the log ratio of predialysis to postdialysis BUN (see previous discussion), is more accurate and patient specific. In addition, anthropometric formulas for V recently were shown to overestimate V in HD patients on average by approximately 15%.[77] However, this systematic overestimation of V tends to protect the patient from underdialysis.

Instead of estimating V, one approach uses modeled V, measured monthly from urea kinetic modeling, as the denominator.[76] If conductivity clearance is measured during the modeled dialysis, it can be used in place of the predicted clearance, eliminating the necessity to record blood flow, dialysate flow, and dialyzer urea mass transfer-area coefficient (K_0A) to calculate K and V. This approach reduces the variance associated with anthropometric V, as discussed; preserves the value of V as a patient-specific measure of body composition; and allows calculation of the patient's G and nPCR.

Another suggested approach uses BSA instead of V as the denominator (see previous discussion of the denominator and V).[78] This measure of dialysis dose is appealing because it tends to equate dialyzer function with native kidney function by using the same denominator, which is closer than V to the universal scaling factor discussed. However, it sacrifices the individual specificity of V and G, relying instead on population averages to calculate BSA from body height and weight.

Although these approaches to measuring the dialysis dose are intriguing and increasingly popular, the HD Work Group believed that compelling evidence for an improvement that would justify changing the current methods for measuring dialysis is lacking. Measurement of the integrated clearance as Kt/V from a simple ratio of predialysis to postdialysis BUN is possible only in patients dialyzed intermittently for whom BUN values fluctuate greatly. These fluctuations provide an opportunity to measure adequacy, V, and nPCR that is unparalleled in other therapeutic settings. The suggested newer methods using on-line clearance and/or a different denominator beg for research that could, in the future, provide evidence for superior performance as a measure of dialysis adequacy (see HD Research Recommendations).

Summary of Methods

Table 4A lists the expressions of dose and methods currently used in clinical practice to measure the delivered dose of dialysis. Preference continues to be given (similar to the previous KDOQI recommendations) to delivered Kt/V_{urea} as the best outcome correlate and to the method of single-pool urea kinetic modeling because of its simplicity, accuracy, and targeting of small-solute clearance, the principal therapeutic effect of HD. While eKt/V theoretically is more indicative of the true dialysis effect, its major advantage is seen during short treatments; it cannot be adjusted directly and it requires measure-

Table 4A. Preferred Measures of the Delivered Dose (in Order of Preference)

For 2 or 3 dialysis treatments per wk
Single pool Kt/Vurea determined by:
Urea kinetic modeling
Simplified multivariable equation
Equilibrated Kt/V (eKt/V)
Bloodless measurements of dialyzer clearance using ionic conductance or dialysate urea monitoring
URR
Double pool Kt/Vurea by formal kinetic modeling (used only for research purposes)
Solute removal index (SRI) from dialysate collections
For more frequent dialysis: a continuous equivalent of kidney clearance
Standard Kt/V_{urea}
Normalized Kt/V_{urea}

ment of spKt/V for estimation from the regression-based formulas shown in Table 4. Because CPR 4 now limits shortened dialysis and for lack of standards, as well as evidence, that eKt/V correlates better with outcome, the KDOQI Work Group, in contrast to the European Standards Group,[12] did not strongly recommend this expression of dose.

LIMITATIONS

To accurately measure Kt/V from the decrease in BUN levels during dialysis, the decrease must be significant, ie, the 2 concentrations (C_0 and C) must be significantly different from one another (ratio $> \sim 1.5$). This means that the dialysis schedule must be truly intermittent to avoid excessive mathematical variance. As the frequency and duration increase, measurement of Kt/V becomes less precise.

Measurement of HD dose and adequacy can be anticipated by both the dialysis staff and the patient. Even if unannounced in advance, modeled or measured dialysis may differ from the typical dialysis because staff are alerted by the predialysis BUN sampling. This issue was addressed by a study that found a higher average blood volume processed during the measured dialysis.[79] In 20% of their patients, the difference was clinically relevant. Quality assurance programs should take this into account by examining elements of the dialysis prescription, including blood volume processed, time on dialysis, and average flow rates during the nonmeasured treatments.

The ideal denominator for dialysis dosage among patients of varying size is the generation rate of uremic toxins because in a steady state of regular dialysis treatments, levels of toxins in the patient are likely to be directly proportional to their generation rates (and inversely proportional to clearance). Therefore, the increase in Kt/V caused by weight loss (lower V) in a dialysis patient with malnutrition likely is a false improvement in dialysis dose. No universally accepted adjustments currently are available to eliminate this potential error, but nephrologists should be aware of the pitfall and consider offering additional dialysis for patients with evidence of malnutrition. Because V is a measure of lean body mass and although using V as the denominator eliminates potential errors that might result from substituting weight in obese patients (presuming that fat is not a source of uremic toxins), it does not eliminate the potential error in malnourished patients. Similarly, an increase in edema fluid or possibly even muscle mass (if edema and muscle do not influence the generation of uremic toxins) is expected to decrease Kt/V, although toxin levels in the patient are not affected. Although some experts are opposed to the notion that delivered dialysis dose be scaled to patient size,[80] it seems intuitive that a one-sized dialysis prescription does not fit all patient ages and sizes. However, it also is possible that the rate of toxin generation has more to do with diet or other factors than body size.

The patient's native kidneys provide functions that cannot be duplicated by the dialyzer and that contribute to patient survival.[81] These benefits, most of which are poorly understood, are not reflected in small-solute clearances, even when adjusted for intermittence.

As dialysis frequency is increased, fluctuations in solute concentration are diminished, reducing the power of urea kinetic modeling and favoring dialysate methods for measuring the dose.

GUIDELINE 3. METHODS FOR POSTDIALYSIS BLOOD SAMPLING

When dialysis adequacy is assessed by using predialysis and postdialysis BUN measurements, blood samples should be drawn by using certain acceptable procedures.

3.1 Both samples (predialysis and postdialysis) should be drawn during the same treatment session. (A)

3.2 The risk of underestimating predialysis BUN level because of saline dilution or by sampling the blood after treatment has begun should be avoided. (A)

3.3 The risk of underestimating the postdialysis BUN level because of access recirculation (AR) should be avoided by first slowing the blood flow through the dialyzer to a rate at which AR is expected to be minimal (100 mL/min) for a period long enough to ensure that unrecirculated blood has advanced to below the sampling port (usually 15 seconds). (A)

3.4 An alternative method is to stop the dialysate flow for a period long enough to increase the dialysate outlet BUN level close to that of the blood inlet BUN level (3 minutes) before obtaining the postdialysis sample. (A)

BACKGROUND

Summary of Updated Changes

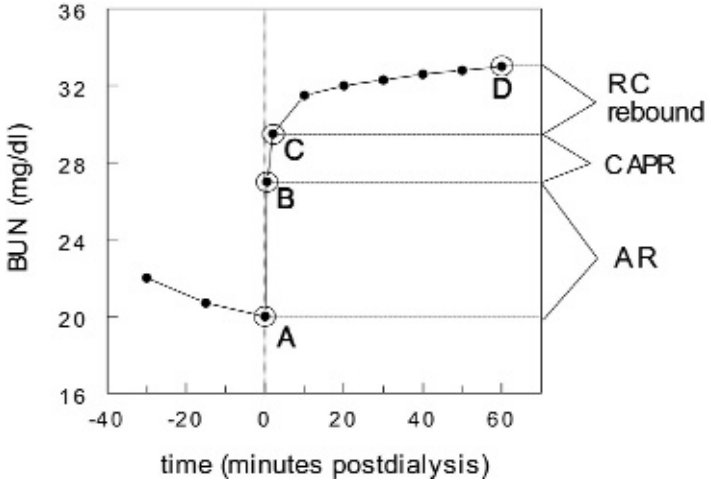
The proper methods of sampling blood for urea nitrogen before and after an HD treatment were detailed in Guidelines 7 through 9 of the previously published KDOQI 2000 HD Adequacy Guidelines.[6] These updated guidelines, 3.1, 3.2, and 3.3, are largely unchanged from the 2000 guidelines, except for minor details. When sampling blood from venous catheters, the volume of the initial aspirate is specified more precisely, and a recommendation is made to discard—instead of routinely reinfusing—the aspirated blood sample. Guideline 3.4, acknowledging the alternative use of the dialysate-stop-flow method, is new.

RATIONALE

As reviewed in the 2000 guidelines,[6] there are 3 components of postdialysis urea nitrogen rebound (see Fig 3). The first is caused by AR, which resolves within seconds after stopping dialysis (point B), the second is caused by CAPR, which resolves within 1 to 2 minutes after stopping dialysis (point C), and the third is caused by entry of urea from relatively undialyzed tissues and body compartments, which we term remote-compartment (RC) rebound. The latter resolves within 30 to 60 minutes after stopping dialysis (point D).

The first focus of these blood-drawing guidelines is to limit the effect of AR on the postdialysis BUN sample because AR causes large overestimations of the true delivered dose and can result in true delivered Kt/V values less than 0.8 (at which level mortality risk is strongly increased) in patients with apparent Kt/V values of 1.4 or greater.[83] Since the KDOQI 2000 guidelines were published, it has become clear that the later rebound caused by CAPR is small[84] and effects of RC rebound are relatively predictable based on

Figure 3. Components of postdialysis urea (BUN) rebound. See text for explanation. Reprinted with permission.[82]



the rate of dialysis.[84,85] In addition, some studies showed that sampling blood about 30 minutes before the end of dialysis can predict the BUN level 30 minutes after the end of dialysis.[86] This method is not recommended in adults because of its relative complexity and because RC rebound is relatively predictable based on the rate of dialysis,[84,85] and—most importantly—because in the presence of AR, the dialysis dose can still be markedly underestimated unless a slow-flow method is used to draw the sample 30 minutes before the end of dialysis.

Predialysis Blood Sampling Procedure (CPG 3.1 and 3.2, see Table 5)

The predialysis BUN sample must be drawn before dialysis is started to prevent this sample from reflecting any impact of dialysis. Dilution of the predialysis sample with saline or heparin must be avoided. Underestimating the predialysis BUN level will result in underestimation of delivered Kt/V or URR, which is not particularly dangerous; however, nPCR then will be underestimated.

Table 5. Recommended Predialysis Blood-Drawing Procedure

A. When using an AV fistula or graft	
1.	Obtain the blood specimen from the arterial needle prior to connecting the arterial blood tubing or flushing the needle. Be sure that no saline and/or heparin is in the arterial needle and tubing prior to drawing the sample for BUN measurement.
2.	Do not draw a sample for use as a predialysis measure of BUN if HD has been initiated.
B. When using a venous catheter	
1.	Using sterile technique, using a 5 mL syringe, withdraw any heparin and saline from the arterial port of the catheter, along with blood, to a total volume of 5 mL.[87,88] Discard the contents of this syringe.
2.	Connect a new syringe or collection device and draw the sample for BUN measurement.
3.	Complete initiation of HD per dialysis clinic protocol.

Table 6. Slow-Blood-Flow Method for Obtaining the Postdialysis Sample

A. Drawing the sample from the blood line sampling port
1. At the completion of HD, turn off the dialysate flow and decrease the UFR to 50 mL/hr, to the lowest TMP/UFR setting, or off. If the dialysis machine does not allow for turning off the dialysate flow, or if doing so violates clinic policy, decrease the dialysate flow to its minimum setting.
2. Decrease the blood flow to 100 mL/min for 15 s (longer if the bloodline volume to the sampling port exceeds 15 mL). To prevent pump shut-off as the blood flow rate is reduced, it may be necessary to manually adjust the venous pressure limits downward. At this point, proceed to obtain your sample. You can either shut off the blood pump before sampling, or leave it running at 100 mL/min while the sample is being drawn.
3. After the sample has been obtained, stop the blood pump (if not already stopped) and complete the patient disconnection procedure as per dialysis clinic protocol.
B. Method that avoids use of an exposed needle: Drawing the sample from the arterial needle tubing using a syringe or vacutainer device.
1. Proceed with steps (1) and (2) as per A above.
2. After the 15 s slow-flow period (a slow-flow period is still required to clear the small volume in the arterial needle tubing of recirculated blood), stop the blood pump. Clamp the arterial and venous blood lines. Clamp the arterial needle tubing. Disconnect the blood line tubing from the inlet bloodline, and attach either a syringe or a Vacutainer with a Luer-Lok type connection to the arterial needle tubing (or arterial port of the venous catheter). Release the clamp on the arterial needle tubing and obtain the blood sample.
3. Proceed with step (3) as in section A above.

TMP: Transmembrane pressure; UFR: Ultrafiltration rate

Postdialysis Blood-Sampling Procedure (CPG 3.3, see Table 6)

Proper timing for acquisition of the postdialysis BUN sample is critical.[6,83] Immediately upon completion of HD, if AR was present, some of the blood remaining in the access and extracorporeal circuit actually is recirculated blood. If the blood sample is drawn immediately upon completion of dialysis, just-dialyzed blood that has recirculated into the access will dilute the sample. The consequence of sampling this admixture is a falsely decreased BUN value and artificially elevated Kt/V and URR.[6,83] Therefore, the amount of dialysis delivered will be overestimated.

Early urea rebound (≤3 minutes after dialysis) may be viewed as a 2-component process.[89–91] The first component is caused by blood recirculation within the access or catheter and is not present in patients without AR. If AR is present, urea rebound from recirculation begins immediately upon completion of HD and resolves in less than 1 minute, usually within 20 seconds. The second component of early urea rebound is caused by CAPR that begins approximately 20 seconds after stopping HD and is completed 2 to 3 minutes after slowing or stopping the blood pump.[90] CAPR refers to the routing of just-dialyzed blood through the veins to the heart, through the pulmonary circuit, and back to the access without the passage of the just-dialyzed blood through any urea-rich tissues.[90–93] It should not occur with a venous access because venous (rather than arterial) blood is sampled; however, some increase in urea concentration during the initial 3-minute time frame may occur because of mixing of urea returning from different organs. The late phase of urea rebound (>3 minutes) is completed within 30 to 60 minutes after the cessation of dialysis. The late phase is a consequence of flow-volume disequilibrium (perfusion or parallel-flow model)[94] and/or delayed transcellular movement of urea (diffusion model)[92,95] (see CPG 2, *Methods of Measuring and Expressing the HD Dose*).

Why the Blood Pump Should Be Slowed Before Sampling. Decreasing blood flow to 100 mL/min reduces the entry of cleared blood into the access and stops AR

(unless there is needle reversal, in which case it still greatly reduces AR). The dead space of the blood tubing attached to the access needle usually is about 3 mL. The dead space in most venous catheters is similar, albeit somewhat less, in the range of 1 to 2 mL. The dead space between the tip of the dialyzer inlet (arterial) blood tubing and sampling port area usually is about 7 to 12 mL, giving a total dead space of 10 to 15 mL, although this should always be measured and known for a given set of blood tubing because in some blood tubing, the sampling port is farther removed from the patient connection. A flow rate of 100 mL/min is about 1.6 mL/s. Therefore, waiting 15 seconds at such a flow rate will ensure that the column of undiluted blood will have moved $1.6 \times 15 = 24$ mL into the blood tubing during the time of reduced blood flow. As long as the volume of tubing between the patient connection and sampling site is substantially less than this 24 mL, the sampled blood should not be contaminated with outflow blood.

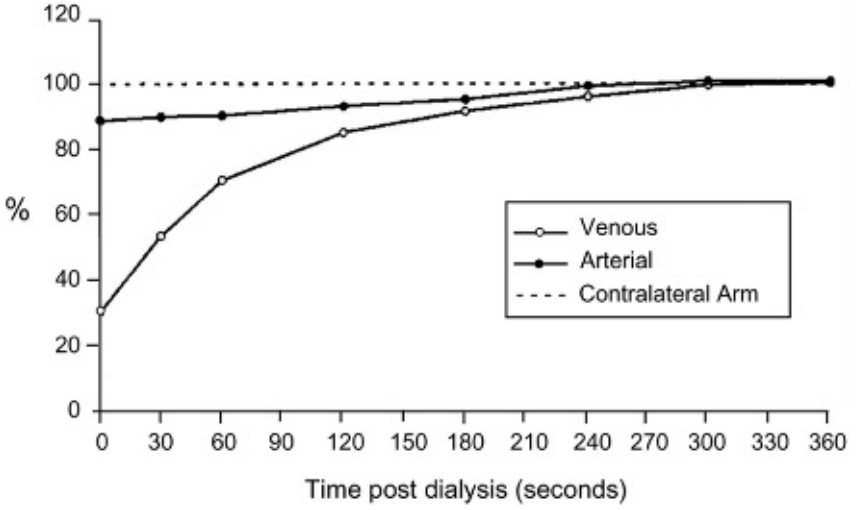
In situations in which the blood is drawn not from a sampling port on the inflow blood tubing, but by attaching a Luer-Lock connector (Becton Dickinson and Co., Franklin Lakes, NJ, USA) to either the venous catheter or arterial needle blood tubing, the dead-space volume to the sampling site is only 2 to 3 mL. However, for simplicity, the Work Group recommended keeping the slow-flow period the same regardless of the site from which blood is sampled.

Stopping Dialysate Flow Before Sampling. A new method for postdialysis blood sampling introduced since the KDOQI 2000 Guideline update was reviewed by the Work Group.[96,97] When dialysate flow is stopped, the dialysate outlet urea concentration starts to approach the blood inlet level, and AR (if present) has a progressively lower dilutional effect on inlet blood flow. With this method, as outlined in Table 7, blood flow must not be reduced because the dialysate, now "trapped" in the dialyzer, needs to equilibrate with blood as quickly as possible. Two studies showed that 5 minutes was adequate to equilibrate the arterial and venous blood tubing samples.[96,97] The Work Group recommendation is to follow the method of Geddes et al.[96] It should be realized that 3 minutes after stopping dialysis, the CAPR component of rebound will be complete and RC rebound will have begun. Hence, a postdialysis BUN sample drawn by using this dialysate method will be slightly higher than that obtained when using the blood method because with the latter, the sample is obtained only 15 seconds after the end of dialysis. This means that the spKt/V obtained by using the stop-dialysate-flow method will (theoretically) be slightly lower in comparison to the slow-the-blood-flow method.

Table 7. Stop-Dialysate-Flow Method of Obtaining the Postdialysis Sample

1. At the completion of HD, turn off the dialysate flow (or put it into bypass) and decrease the UFR to 50 mL/hr, to the lowest TMP/UFR setting, or off.
2. Wait 3 min. Do NOT reduce the blood flow rate during this 3-min period.
3. Obtain the blood sample, either from the sampling port on the inlet bloodline, or from the arterial needle tubing or from the arterial port of the venous catheter if using the needle-free method as described in Table 6, part B. If sampling from the inlet bloodline, it does not matter if you stop or do not stop the blood flow while this sample is being taken. It probably is best to stop the blood pump prior to sampling. In the stop-dialysate-flow method, slowing the blood flow prior to sampling should not be done.
4. After the sample has been obtained, return the patient's blood in the bloodlines and dialyzer per protocol.

Figure 4. Stop-dialysate method for postdialysis blood sampling. Mean arterial and venous blood urea concentrations after stopping dialysate flow are expressed as a fraction of the blood urea concentration in the contralateral arm at time zero (n = 10). The data suggest that, for practical purposes, 3 minutes after stopping dialysate flow, equilibration has occurred between inlet and outlet blood. Reprinted with permission.[96]



Use of a 5-minute waiting period resulted in a 2% decrease in measured value for URR (Fig 4). [96] Because of the rebound considerations discussed and based on data in Fig 4, the Work Group decided that a 3-minute waiting period was sufficient. By that time, dialyzer inlet and outlet samples have nearly equilibrated.

LIMITATIONS

The stop-dialysate-flow method has not been validated during pediatric dialysis. If a large dialyzer is used at a relatively lower blood flow rate, the dialyzer outlet blood may still have a substantially lower urea concentration than inlet blood after 3 minutes of stopping dialysate flow.

GUIDELINE 4. MINIMALLY ADEQUATE HEMODIALYSIS

4.1 Minimally adequate dose:
The minimally adequate dose of HD given 3 times per week to patients with K_r less than 2 mL/min/1.73 m^2 should be an spKt/V (excluding RKF) of 1.2 per dialysis. For treatment times less than 5 hours, an alternative minimum dose is a URR of 65%. (A)

4.2 Target dose:
The target dose for HD given 3 times per week with K_r less than 2 mL/min/1.73 m^2 should be an spKt/V of 1.4 per dialysis not including RKF, or URR of 70%. (A)

4.3 In patients with residual urea clearance (Kr) greater than or equal to 2 mL/min/1.73 m^2, the minimum session spKt/V can be reduced. One method of minimum dose reduction is described in CPR 4.4. In such patients, the target spKt/V should be at least 15% greater than the minimum dose. (B)

4.4 Missed and shortened treatments:
Efforts should be made to monitor and minimize the occurrence of missed or shortened treatments. (B)

RATIONALE

Minimally Adequate Dose (CPG 4.1)

The present adequacy guideline for a minimally adequate dose remains unchanged from the previous (2000) guidelines.[6] In deciding whether this guideline needed to be changed, the committee considered 3 lines of evidence. The first was results of the primary analysis of the NIH HEMO Study, published in 2002.[1] The committee also had access to as-treated results of the HEMO Study, which were published at the time the draft guidelines were released in November 2005.[98] This report was judged to be of some importance because it identified a dose-targeting bias in the analysis of delivered therapy versus mortality in cross-sectional data sets, which potentially impacts on the weight of evidence derived from such data sets. The second was a series of articles suggesting that dosing of dialysis should not be based on URR or its derivative, Kt/V (which essentially is volume of blood cleared divided by the modeled urea volume, V), but on the volume of blood cleared (Kt) only.[78,99–101] The third was a series of analyses of delivered dose (ie, URR) versus mortality based on either the USRDS-Medicare data set or the Fresenius Medical Care subset of these data.[102–104]

HEMO Clinical Study: Primary (Randomized) Results. Primary results of the HEMO Study, which randomized patients to a delivered eKt/V of 1.16 versus 1.53, equivalent to URR values of about 63% versus 75% or spKt/V values of about 1.3 versus 1.7, revealed little evidence to support increasing the dose of dialysis beyond the current (2000) KDOQI recommendations, respectively.[6] The lack of benefit, without even a trend that was close to statistical significance, appeared not only in the primary outcome of mortality, but

also in a variety of main secondary composite outcomes relating to various causes of hospitalization combined with mortality. Furthermore, analysis of minor secondary composite outcomes dealing with nutritional measures—including changes in weight and serum albumin levels,[105] as well as QOL measures[106]—also failed to support a beneficial effect of increasing the dose of dialysis. Of all trials evaluated, the HEMO Study was by far the largest, and its randomized design and measurement of hard outcomes were given an enormous weight in determining whether the 2000 KDOQI HD Adequacy Guidelines needed to be changed. The Work Group realized that the recently published European guidelines recommended substantially higher minimal doses of HD based on an eKt/V measure, corresponding to spKt/V minimum targets of about 1.4 to 1.5.[12]

HEMO Clinical Study: As-Treated Results. The HEMO dose-versus-mortality question also was assessed within each treatment arm, measuring the effects of actual delivered dose over time versus mortality.[98] This study identified a dose-targeting bias and suggested that patients in a cross-sectional analysis receiving less dialysis are also at greater risk for death. This increased death risk was of a high magnitude and was incompatible with a biological effect of dose. Although conditions of the 2 HEMO Study arms were not representative of how dialysis is prescribed in the field, documentation of such a strong potential dose-targeting bias (which may be operative in cross-sectional studies, albeit to a lesser degree) convinced the Work Group members to place less weight on dose-versus-mortality relationships derived from observational studies despite the large numbers of patients included in such studies.

Studies Advocating Alternate Measures of Urea-Based Adequacy. These studies are discussed in more detail in CPG 2, *Methods for Measuring and Expressing the HD Dose.* Since the 2000 KDOQI HD Adequacy Guidelines were published, 1 group of investigators in particular, using data derived from Fresenius Medical Care North America patients in the United States, argued that dose of dialysis should not be factored by modeled V.[78,100,101] The arguments against using URR or its derivative Kt/V fall into 2 general categories: (1) doing so may result in relative underdialysis of women and small patients of both sexes, and (2) because modeled V is itself a predictor of mortality, use of dialysis dose factored by V may confound dialysis dose-versus-mortality relationships found in cross-sectional studies in complex and not always predictable ways. A secondary analysis of the intent-to-treat results of the HEMO Study suggested that the higher dose of dialysis may result in better survival in women, who also tended to be smaller than the men in that particular trial.[13] The Work Group decided, based on suggestive evidence, that more dialysis (beyond 2000 KDOQI levels) may be better for women and, perhaps, smaller patients, but that the level of evidence did not reach a point at which the existing guideline should be changed. Hence, 2 CPRs were derived suggesting that more dialysis in women and/or in smaller patients might be beneficial (see Section II). Despite the theoretical arguments, as well as attempts to address confounding effects of V in cross-sectional data sets, the committee believed that, at present, the data are not compelling enough to depart from the 2000 recommendation to follow small-molecule clearance using Kt/V.

Given the increased use of conductivity to measure clearance during the dialysis session, the Work Group also considered using an anthropometric volume as the clearance denominator when clearance was measured by conductivity. Using an anthropometric volume as denominator was speculated to result in a more stable denominator, less affected by errors in predialysis and postdialysis urea nitrogen determinations. For example, ($K_{ecn} \times T/V_{ant}$, where V_{ant} = anthropometrically-estimated total body water distribution volume) could be used instead of Kt/V urea. The Work Group's conclusion was that there were not sufficient data comparing sequential dialysis adequacy measures by using both conductivity and urea kinetics in the same patients to make such a major revision, although it was recognized that from a quality-assurance perspective, it would be less challenging to ensure a constant dialysis dose given a more constant denominator. Concerns also were raised about altered modeled to anthropometric urea volume ratios in individual patients, although given the relative flatness of the adequacy to mortality curve, this issue may be of secondary importance.

Another potential strategy discussed was to normalize the dialysis amount to a denominator based on BSA as opposed to urea volume, whether the latter was derived from modeling or anthropometrics. For example, this is accomplished easily by multiplying the target Kt/V value by $3.27 \times V/V^{0.667}$ (V raised to the 2/3 power). Such a correction method (developed by the Frequent HD Network investigators) gives the same dialysis dose when V = 35 L, but then augments the dose when V is less than this amount and reduces the dose when V is larger, giving, in effect, a dose based on BSA instead of V. Again, for lack of definitive clinical outcomes evidence supporting this approach, it was left for perhaps a future revision of the guidelines when more data might be available.

Dose-Related Mortality in Large Observational Data Sets. Since the KDOQI 2000 HD Adequacy guidelines were published, a number of studies, including analyses of USRDS Annual Data Reports, continued to examine the relationship between dose of dialysis and mortality. Most, but not all, observational studies reported dose in terms of either spKt/V or URR. The dose-versus-mortality relationship was examined as a function of race and sex[57,104] and as influenced by various measures of body size[102,103] and nutritional status.[99] Because the general median spKt/V increased over time, these analyses included much larger samples of patients receiving higher doses of dialysis. Most of these analyses suggested that increasing the dose of dialysis above the target recommended in the 2000 guidelines to levels targeted in the high-dose arm of the HEMO Study (spKt/V $\sim$ 1.7) should decrease mortality by a substantial amount (Table 8). However, the lack of concordance between these observational results and negative results of the HEMO Study, coupled with the dose-targeting bias identified in the as-treated analysis of HEMO Study patients, restrained the Work Group from recommending a global increase in recommended spKt/V for patients dialyzed 3 times per week.

Renal Clearance Compared With the 2000 Guidelines. The 2000 KDOQI HD Adequacy Guidelines were applied to patients with a K_r less than 5 mL/min/1.73 m^2, for which K_r is defined as the average of urea and creatinine clearances. In the present guidelines, the committee decided to use urea clearances for the purpose of specifying minimally

Table 8: Effect of HD Dose on Mortality

Author, Year	Study design	N	Follow-up (maximum)	Applicability	Predictor	Results			Quality
						Effect Size	95% CI	P Value	
Eknoyan, 2002[1]	RCT	1846	(6.6 yr)	↑↑↑	High dose (1.53±0.09) vs. Low dose (1.16±0.08)[a]	RR=0.96	0.84, 1.10	NS	●
Depner, 2004[13] HEMO	RCT	Men: 1037	nd	↑↑↑	High vs. Low Dose	RR=1.16		NS	●
		Women:809				RR=0.81		0.02	
Termorshuizen, 2004[81]	Prospective	740	(4.5 yr)	↑↑↑	spKt/V per week (per increase of 1/wk)	RR=0.76	0.64, 0.92	0.004	●
Port, 2004[104] DOPPS	Prospective	Men: 6165	nd	↑↑↑	eKt/V: per 0.37	RR=0.93		NS	○
		Women:4651				RR=0.80		<0.001	
Port, 2004[104] CMS	Retrospective cohort	Men: 38,098	(32 mo)	↑↑↑	URR: >75% vs. 70-75%:	RR=0.96		NS	○
		Women: 36,022				RR=0.85		<0.0001	
Port, 2002[102]	Retrospective cohort	45,967	(24 mo)	↑↑↑	URR: >75% vs. 65-70%	RR=0.76		<0.0001	○
					URR: 70-75% vs. 65-70%	RR= 0.86		<0.0001	
Wolfe, 2000[133]	Retrospective cohort	9166	(2 yr)	↑↑	eKt/V per SD increase (mean=1.01, SD=0.19)	RR%= -12%		0.0001	○
Chertow, 1999[99]	Retrospective cohort	3009	(18 mo)	↑↑	URR:				○
					Q1 (<60%)	RR=1.67	1.17, 2.38	NS	
					Q2 (60.0 to 64.1%)	RR=1.34	0.94, 1.91	NS	
					Q3 (64.1 to 67.4%)		Reference		
					Q4 (67.4 to 71.0%)	RR=1.12	0.78, 1.61	NS	
					Q5 (>71.0%)	RR=1.12	0.79, 1.60	NS	
					Kt:				
					Q1 (31.0)	RR=1.39	0.99, 1.95	NS	
					Q2 (38.0)	RR=1.19	0.84, 1.68	NS	
					Q3 (42.5)		Reference		
					Q4 (47.6)	RR=1.02	0.72, 1.45	NS	
					Q5 (57.2)	RR=0.98	0.68, 1.41	NS	
Leypoldt, 1999[274]	Retrospective cohort	1771	nd	↑↑	spKt/V: per 0.1U increase	RR=0.95		<0.05	○
Salahudeen, 2003[287]	Retrospective cohort	1151	(9 mo)	↑↑	spKt/V: >2.4 vs. 1.2-1.3	RR=2.5		<0.05[b]	○
					spKt/V: >1.68 vs. 1.23-1.39	RR=0.9	0.4, 2.0	NS	
Woods, 2000[275]	Retrospective cohort	All: 715	(5 yr)	↑	Kt/V: per 1.0 increase	HR=0.047	0.037, 0.059	<0.00005	○
		Non-diabetic: 644				HR=0.051	0.038, 0.067	<0.00005	

a. Achieved dose
b. Univariate analysis
c. Kt predictor= URR was converted to a single-pool Kt/V (spKt/V) and then the spKt/V multiplied by V estimated by bioelectrical impedance analysis (BIA) to derive a clearance x time product (Kt, in L).

Table 9. Fraction of Treatments With an spKt/V Greater Than 1.2 When Targeting 1.2 to 1.4 per Dialysis

	Achieved Kt/V averaged over k treatments*			
Target Kt/V	k = 1	k = 2	k = 3	k = 4
1.20	0.51	0.48	0.47	0.47
1.25	0.66	0.68	0.68	0.69
1.30	0.79	0.82	0.84	0.84
1.35	0.87	0.90	0.93	0.93
1.40	0.92	0.95	0.97	0.97

Data shown for a single treatment (k = 1) and for averaging over k treatments.
*Greene et al. Proceedings of the XVth International Congress of Nephrology, Buenos Aires, Argentina, May 2 through 6, 1999.[69A]

adequate urea fractional removal. This allows more accurate measurement of protein catabolism in patients with significant K_r and an opportunity to combine K_r with K_d (see CPG 2). Urea clearance of 3 mL/min corresponds approximately to an average of urea and creatinine clearances of 5 mL/min. In the present guidelines, this number was reduced to 2 mL/min of normalized urea clearance to enable some decrease in dialysis dose for patients with moderate degrees of RKF, as discussed in the accompanying CPR. A more complete discussion of why this "step" strategy was adopted, rather than the addition of residual clearance as a continuous function, is detailed in the accompanying CPR.

Target Dose (CPG 4.2)

The KDOQI 2000 HD Adequacy Guidelines specified a target spKt/V of 1.3, with a minimally adequate dose of 1.2 per dialysis given 3 times per week. During the course of measuring the dose of therapy many times in each patient enrolled in the HEMO Study, the variability of modeled volume and hence of spKt/V was determined accurately. The within-patient coefficient of variation for single-pool V in the HEMO patient data set was close to 10%. The relationship between target Kt/V and subsequent achieved Kt/V is shown in Table 9.

As shown in Table 9, the previous recommendations to target 1.3 would result in about 21% of treatments at any given time apparently being less than the Kt/V minimum target of 1.21 (the fraction > 1.2 is 0.79, so 0.21, or 21%, would be < 1.2). Thus, it appears that targeting 1.3 would result in needless prescription modifications and/or troubleshooting. Targeting therapy at an spKt/V of 1.4 and averaging results from 3 monthly measurements of adequacy results in a much greater proportion of treatments (in the range of 97%), greater than the minimum 1.2 adequacy target. Setting the target dose of dialysis to 1.4, rather than 1.3, also seemed to be justified given suggestive results (not yet qualifying for guideline-generating status) that subsets of patients might benefit from higher doses of dialysis.

Avoiding Missed Treatments (CPG 4.3)

Measurement of fractional urea removal during a single dialysis treatment obviously is not a monthly average of dialysis adequacy and has validity only if dialysis treatments are delivered reliably 3 times per week on a regular basis. A number of studies document that the number of missed and/or shortened dialysis treatments in US dialysis patients (4% missed treatments per month) is more than the number missed by their counterparts in other countries, such as Japan.[107] Whereas the KDOQI 2000 HD Adequacy Guidelines

suggested increasing the frequency of measuring Kt/V or URR in patients for whom treatments frequently were shortened or missed, they did not address the issue of monitoring and minimizing the occurrence of missed and shortened treatments. A number of studies suggested that poor compliance in HD, especially in terms of number of missed treatments, is an important predictor of mortality and hospitalizations.[14–16] For this reason, the Work Group believed that every dialysis center should have a mechanism in place to monitor and minimize the occurrence of missed and shortened dialysis treatments.

LIMITATIONS

The main limitation to recommending adequate dosing of dialysis in patients following a thrice-weekly schedule is the difficulty performing randomized studies, as well as multiple confounding issues related to analysis of dose-mortality relationships in observational studies. In the Work Group's opinion, data from the HEMO Study suggested that the dose-benefit relationship for values of spKt/V in the current clinical setting are relatively flat at greater than the recommended minimum value of 1.2 thrice weekly. Many patient subgroups and perhaps all patients might benefit from more dialysis, but it seems that benefits would be derived primarily from extending dialysis treatment time markedly or moving to a more frequent dialysis schedule, as opposed to simply increasing urea Kt/V.

GUIDELINE 5. CONTROL OF VOLUME AND BLOOD PRESSURE

There is ample evidence in the non-CKD population that optimal control of blood pressure influences mortality. In the HD population, available evidence indicates that control of a patient's fluid volume influences outcome. Volume and blood pressure are linked; thus, it is important to optimize ultrafiltration and dry weight to control blood pressure in an effort to improve patient outcome.

5.1 The ultrafiltration component of the HD prescription should be optimized with a goal to render the patient euvolemic and normotensive. This includes counseling the patient on sodium and fluid restriction, adequate ultrafiltration, and the use of diuretics in patients with RKF. (A)

5.2 Daily dietary sodium intake should be restricted to no more than 5 g of sodium chloride (2.0 g or 85 mmol of sodium). (A)

5.3 Increasing positive sodium balance by "sodium profiling" or using a high dialysate sodium concentration should be avoided. (B)

RATIONALE

The volume status of a maintenance dialysis patient is mainly a function of sodium intake, water intake, urine output, and removal of excess fluid by ultrafiltration during dialysis. Because cellular membranes are freely permeable to water, the osmotic gradient generated by the addition of dietary sodium to the ECF compartment causes water to move from cells into the ECF space, thus expanding ECF volume at the expense of the intracellular fluid compartment. The increase in ECF osmolality stimulates the thirst center of the hypothalamus, increasing water intake. Thus, the combined influence of both positive sodium and water balances causes expansion, primarily of the ECF volume.[108] Such volume expansion can be especially marked in dialysis patients with poor RKF.

Poor volume control can exacerbate hypertension and its myriad detrimental effects on the cardiovascular system.[109-112] Early reports of risks associated with excessive sodium and water were inconclusive, but analysis of USRDS Waves 3 and 4, when adjusted for comorbidity, showed that weight gain between dialyses of more than 4.8% (ie, 3.4 kg in a 70 kg person), a reflection of excessive sodium and water intake, is associated with increased mortality.[113] Although a precise definition of dry weight is not possible in each patient, methods have been described for controlling volume and blood pressure and are reviewed here. A thorough examination of the approach to deriving a true "dry" weight is beyond the scope of the Work Group. The reader is referred to standard dialysis texts for detailed information.

Achievement of Optimal "Dry" Weight (CPG 5.1)

A patient's true dry weight, defined as the weight when fluid volume is optimal, can be determined accurately, but the method is not readily available in clinical settings (eg, use of multiple-frequency bioimpedance spectroscopy).[114] Instead, dry weight usually is determined clinically by evaluating level of blood pressure, evidence of fluid overload, and the patient's tolerance of ultrafiltration aimed to arrive at the estimated target weight.[115]

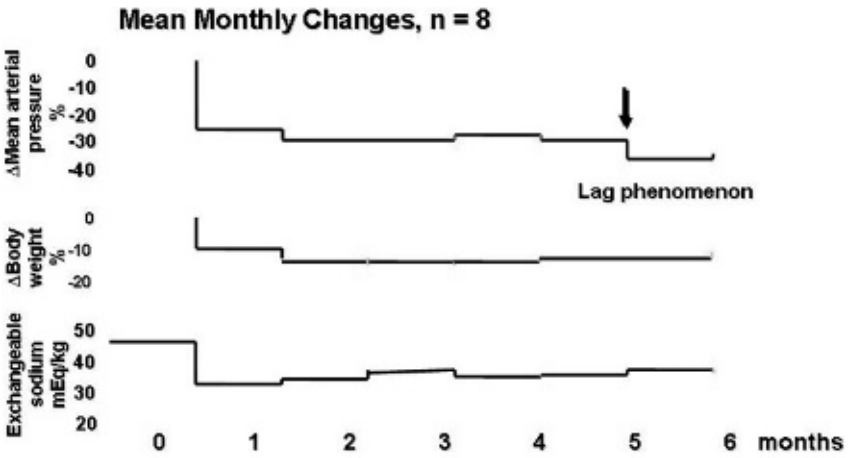
It should be noted that a patient can have fluid excess in the absence of gross clinical evidence of volume expansion,[116] a phenomenon termed "silent overhydration."[117] During dialysis, as the patient's dry weight is approached, the rate at which the vascular compartment refills from fluid in the adjacent tissue spaces is reduced.[118] If UFR is reduced toward the end of dialysis, the reduced compensatory refilling process may be adequate to support the patient's depleted blood volume, thereby avoiding hypotension and muscle cramping. When the blood volume is refilled and blood pressure improves, more rapid ultrafiltration can be resumed. For a fluid-overloaded dialysis patient, this step-by-step process of identifying, or "probing," for the true dry weight through ultrafiltration—but without inducing hypotension—should be accomplished gradually over a number of dialysis treatments (usually over 4 to 12 weeks, but it may require as long as 6 to 12 months) until evidence of fluid overload is in abeyance.[119–121] For patients with diabetes mellitus (autonomic dysfunction) or cardiomyopathy, this process of approaching the dry weight may take longer because plasma refilling can be low even in the presence of an expanded volume.

From the very beginning of the dialysis therapy, concomitant with ultrafiltration probing, dietary sodium should be restricted and use of a high dialysate sodium concentration and sodium profiling should be avoided. While decreasing the patient's fluid volume, net fluid losses ideally should not exceed 1 to 2 kg/wk, and by restricting dietary sodium and fluid intake, weight gain between dialyses should not exceed 1 kg during the week and 1.5 to 2 kg during the weekend.[121] It should be noted that during this dry weight–probing stage, in 90% of patients, ECF volume becomes normal within a few weeks, but the elevated blood pressure continues to decrease for another 8 months or longer. See Fig 5 for a description of this "lag phenomenon."[122–125] As patients lose excess fluid and their hypertension improves, therapy with antihypertensive medications can be systematically tapered or discontinued.[121]

Tolerance to ultrafiltration varies among patients. The slow approach to achievement of dry weight is appropriate for most patients, but for patients with cardiac failure or severe complication-associated hypertension, more aggressive ultrafiltration may be required acutely.[126] Some patients may require slow ultrafiltration during a longer time than 4 hours 3 times weekly.[115] To improve fluid removal during dialysis and reduce morbidity, monitoring blood volume during HD has been recommended. However, use of monitoring devices has met with varying degrees of success; some investigators have obtained satisfactory results,[127–130] whereas other have had disappointing results.[131] Further studies are required to clarify this important issue.

Hypotension during dialysis has many adverse effects and potential life-threatening consequences. By impairing tissue perfusion, low blood pressures can compromise dialysis adequacy.[132] Hypotension induced by overzealous ultrafiltration also may contribute to loss of RKF and, in predisposed patients, coronary and/or cerebral ischemia.[121] To avoid hypotension, dry weight should be systematically reevaluated after each dialysis treatment. It was suggested that a dialysis log summarizing the relevant information, such as body weights, blood pressures, and intradialytic incidents, is essential to provide a longitudinal dynamic view of ECF volume and blood pressure changes.[133] Dry weight may

Figure 5. Illustration of the "lag phenomenon." The secondary decrease in blood pressure seen at 5 months unassociated with a change in ECV was observed in all 8 patients studied. Reprinted with permission.[125]



change, for example, when a newly dialyzed patient becomes less uremic, regains appetite, and gains muscle and nonfluid weight (reflected by an increase in serum creatinine level), or when a patient has an intercurrent illness and loses muscle and tissue weight.

Hypertension: Prevalence, Pathogenesis, and Risks (CPG 5.1)

It is noteworthy that 60% to 90% of maintenance HD patients have hypertension.[41,109,134–138] Despite the use of multiple medications, hypertension in these patients often is poorly controlled.[109,111,124,136,139] For example, among the first 1,238 maintenance HD patients enrolled in the HEMO Study, less than 30% had blood pressures that were considered normotensive by the Joint National Committee (JNC) VI standards.[111] In another study of 2,535 clinically stable adult HD patients, 86% were found to be hypertensive. Within this hypertensive group, only 30% had their blood pressure under adequate control, 58% were inadequately treated, and 12% were not treated at all.[109]

With regard to the pathogenesis, it generally is recognized that the majority of hypertensive HD patients develop hypertension because of fluid overload secondary to sodium and water retention.[123,133,140–142] A high predialysis or interdialysis blood pressure may be related to excessive sodium and water ingestion during the interdialysis period,[126,136] a high dialysate sodium level,[143,144] or sodium profiling,[145] whereas a high postdialysis blood pressure may reflect inadequate achievement of dry weight.[113,146] There may be exceptions to these simple explanations of the effects of sodium and water retention on a patient's blood pressure. For example, blood pressures in a small number of patients with CKD stage 5 were found to respond less readily compared with the majority when challenged with similar degrees of fluid retention.[112,134] Conversely, reduction of fluid excess in a hypervolemic and hypertensive dialysis patient may not bring about a prompt decrease in blood pressure until ECV is less than a certain threshold value. These clinical

observations suggest that the relationship between ECV and blood pressure in some patients may be sigmoidal, rather than linear, and that volume overload leads to an increase in blood pressure only when physiological autoregulation can no longer cope with the fluid excess.[147]

For some patients, the conventional dialysis time is too short for their ultrafiltration requirements to be readily fulfilled. Attempts to accelerate ultrafiltration in these patients may precipitate hypovolemia and hypotension. Normal saline frequently is administered and ultrafiltration is slowed or discontinued, at least temporarily. As a consequence, at the end of the dialysis session, not only has the originally targeted fluid excess not been removed, but the infused saline also has expanded ECV further. More sodium and water will accumulate during the succeeding interdialysis period, contributing further to a chronic state of baseline volume expansion in association with persistent hypertension.

It should be noted that each 10 mm Hg increase in mean arterial blood pressure is correlated independently with the development of progressive concentric LVH, de novo ischemic heart disease, and de novo congestive cardiac failure.[148] The leading cause of death in maintenance HD patients is CVD,[149] which is responsible for at least 50% of HD deaths in the United States.[112] Apart from fluid overload, there are other significant pathogenic factors for hypertension in dialysis patients,[150] such as arterial stiffness[151,152] caused by arteriosclerosis, salt-related reduction in nitric oxide formation,[153–155] sympathetic nervous system overactivity,[156] activation of the renin-angiotensin system,[157] presence of other vasoconstrictors,[126] lack of vasodilators,[126] erythropoietin therapy,[158] genetic predisposition,[112] and other as yet poorly defined causes. Although it is generally recognized that hypertension requires control in hypertensive dialysis patients,[110,147,159,160] the ideal target blood pressure is unknown at present.[161] In patients with reduced vascular and cardiac compliance, blood pressure goals may need to be higher. Vigorous contraction of plasma volume in such patients should be avoided to allow adequate tissue perfusion during ultrafiltration when hypotension is prone to occur.[161] However, some have recommended that attempts be made to decrease these high pressures as much as possible to achieve optimal survival.[162] Finally, some dialysis patients with low predialysis blood pressures also have a high mortality rate.[148,163,164] Risk for death in these patients may reflect cardiac failure, coronary artery disease, malnutrition, inadequate dialysis, or other serious illnesses that can decrease blood pressure.[110,161,165] It is likely that the cardiovascular problems in some of these patients result from poorly treated prior hypertension. Thus, there is every incentive to control blood pressure as early as possible before cardiac damage leads to permanent hypotension and an almost certain early death.[166]

In a small number of patients, blood pressure paradoxically increases after dialysis. The mechanism of this elevation is not fully understood.[147] Some hypertensive patients for whom blood pressure increases while fluid is removed during dialysis may respond to still more fluid removal by undergoing repeated isolated ultrafiltration sessions, with eventual better blood pressure control.[167] However, attempts to remove excess fluid from these patients by using ultrafiltration should be conducted with special care.[147]

Recommended Sodium Intake (CPG 5.2)

The normal daily sodium chloride intake in the United States varies from 5.8 to 17.4 g (2.3 to 6.9 g [100 to 300 mmol] of sodium),[168] while both the American Heart Association[169,170] and Institute of Medicine[171] recommend a daily tolerable upper intake level for sodium chloride of no more than 5.8 g (2.3 g [100 mmol] of sodium) for the average healthy adult. The Institute of Medicine also recommends that because older individuals, African Americans, and people with chronic diseases, including hypertension, diabetes, and kidney diseases, are especially sensitive to the blood pressure–increasing effects of salt, they should consume less than the tolerable upper intake level. The European Society of Hypertension and European Society of Cardiology recommend a daily sodium chloride intake of 4.7 to 5.8 g (1.8 to 2.3 g [80 to 100 mmol] of sodium) for patients with arterial hypertension.[172] Finally, use of a low-sodium chloride diet, namely, less than 5.8 g (2.3 g [100 mmol] of sodium) also was found to decrease blood pressure in individuals without hypertension.[173]

Thus, the daily sodium chloride intake suggested for dialysis patients (namely, no more than 5 g [ie, 2.0 g [85 mmol] of sodium]) is consistent with recommendations for healthy adults by US health research groups and for patients with essential hypertension by European health organizations. It also is recommended for dialysis patients by various investigators.[133,141,174–176] A 5-g sodium chloride diet in a 70 kg anuric compliant patient should bring about a 1.5-kg average interdialysis weight gain on a conventional thrice-weekly regimen.[141] Most dialysis patients should be able to tolerate this degree of ultrafiltration requirement. A more stringent daily sodium chloride limitation amounting to 2.5 to 3.8 g (1 to 1.5 g [43 to 65 mmol] of sodium) has been recommended for hypertensive dialysis patients.[121,126] In patients who happen to lose appreciable amounts of sodium through either RKF or extrarenal routes, sodium restriction can be modified and tailored to those losses. Patients who are accustomed to a more liberal sodium intake might lose their appetites and become malnourished if sodium restriction is instituted too abruptly and too strenuously. In such patients, sodium limitation can be introduced gradually to provide ample time for taste adjustments. Most patients find that they do not miss the sodium if they cut back gradually.[176A] For patients who cannot tolerate sodium restriction at all, to combat sodium and water excess, more prolonged and/or more frequent dialysis treatments (including periodic isolated ultrafiltration) may be required (see *Prolonging Dialysis Treatments*).

When observing a low-sodium diet, in addition to refraining from adding salt during cooking and at the dining table, canned, processed, and salty-tasting food should be avoided.[172,175] A low-sodium diet does not equate to tasteless food. Many varieties of flavor enhancers are available to make food more appealing and palatable.[143] Moreover, after exposure to salt restriction for 8 to 12 weeks, the appeal of low-sodium foods in both normotensive and hypertensive individuals is enhanced.[177] Sodium restriction does not require a reduced intake of other essential nutrients.[178]

Sodium Restriction and Blood Pressure Control (CPG 5.2)

That excessive sodium intake can aggravate hypertension and adequate sodium restriction can prevent or ameliorate hypertension is well known.[169] As early as the middle of

the last century, limiting daily sodium intake of non-CKD hypertensive patients with a rice and fruit diet was shown to reduce ECF volume and blood pressure during a period of weeks as excess sodium was excreted in urine.[179] This observation pertaining to the benefit of sodium limitation may relate to the rarity of hypertension among individuals of populations living in very remote areas who consume a low-sodium diet (median daily intake, 17 to 51 mmol).[180]

Among dialysis patients, myriad observational and interventional studies of patients with CKD have shown that restricting sodium intake is an essential tool for volume and blood-pressure control.[124,125,140,141,165,175,181–192] Apart from its effect in nonuremic hypertensive patients, a sodium-poor rice and fruit diet also was shown to improve the hypertension of patients with renal failure.[193,194] These observations echo those in PD patients, for whom decreasing sodium in the diet is crucial for the achievement of dry weight and effective control of blood pressure.[195]

Since infancy, most of us are accustomed to consuming a larger quantity of salt than we need.[196] Restricting salt intake in HD patients is tantamount to requiring them to change their customary lifestyle. Changing one's lifestyle is always a difficult undertaking. However, moderating one's sodium intake is a small price for a patient with CKD to pay if one wishes to avoid the devastating effects of relentless excess sodium and water accumulation on morbidity and mortality.

Prolonging Dialysis Treatments. Elevated blood pressures can be decreased satisfactorily with aggressive ECF volume control, achieved by limiting sodium intake and performing adequate ultrafiltration.[182] Success using this strategy has been reported in studies from Tassin, France, showing that hypertension is improved substantially with a combination of dietary sodium limitation (85 to 100 mmol/d of sodium) and dialyzing slowly for 8 hours 3 times per week.[197] Sodium limitation decreased patients' average weight gain between dialyses to 1.7 kg, less than 3% of mean BW.[133] Both the limited weight gain (ie, ultrafiltration requirement) and long period of ultrafiltration combined to ensure that symptoms during dialysis were minimized and dry weight was achieved.[133] Upon initiation of HD treatments, 89% of patients were hypertensive despite therapy with antihypertensive medications. However, after 3 months of the described strategy, only 5% of those patients still required the use of such medications.[197] Of course, because the Tassin patients were dialyzed longer than patients treated with a conventional regimen, it could be argued that these patients fared better because they had better removal of small and middle molecules, improved nutrition, and better phosphate control. However, a comparison study of mortality rates in conventionally dialyzed patients from Nottingham, United Kingdom, concluded that the improved control of blood pressure was the most likely and predominant cause of better results shown by the Tassin patients.[198]

It should be noted that adequate control of blood pressure as a consequence of dietary sodium restriction (<100 mmol/d of sodium) and appropriate ultrafiltration with[175] or without[185,199] a low-sodium dialysate (135 mmol/L) also was shown in patients treated with a conventional thrice-weekly (4 to 5 hours per treatment) dialysis regimen. In addition to blood pressure control, patients also showed regression of LVH and a decrease in left atrial and left ventricular systolic and diastolic pressures.[185,199]

For conventionally dialyzed patients (3 sessions per week, ≤4 hours per session) who are still overloaded despite maximally tolerable ultrafiltration, the recently proposed: (1) short-daily (2 to 3 hours for each treatment, 6 or 7 treatments per week) regimen;[200–202] (2) long (8 hours for each session) nocturnal thrice-weekly regimen;[197,203] and (3) long (8 hours for each session) nocturnal (6 to 7 nights per week) regimen[204,205] all were reported to remove excess fluid and improve hypertension satisfactorily.[110] A longer weekly treatment time (5 hours per session, 3 times per week) also was shown to cause less hypotension during dialysis and less postdialysis postural hypotension compared with its shorter counterpart (4 hours per session, 3 times per week).[206] Alternatively, periods of isolated ultrafiltration can be added to a standard treatment regimen.[199]

Dietary Water Restriction. When a patient is advised to restrict sodium intake, does he or she need to be advised to limit water intake too? It was suggested that attempts at water restriction commonly are futile if sodium limitation is not observed simultaneously. Reducing a patient's water intake alone is not prudent most of the time because the increased ECF osmolality brought about by the excessive sodium ingestion stimulates thirst, followed by water consumption and hence isotonic fluid gain.[207,208] Advising patients to limit their water intake without curtailing their sodium intake will cause suffering from unnecessary thirst. Some of these patients may even feel guilty if they fail to resist the urge to drink in the face of marked thirst.[143] However, although excessive water intake accompanies the ingestion of excess salt, other factors can have a role in stimulating drinking. Such factors include hyperglycemia, elevated blood angiotensin levels, and ingestion of such drugs as clonidine.[209] Thus, to ensure complete safety, patients should be watched carefully to make sure they do not accumulate more fluid than recommended.

Pathogenesis of the Lag Phenomenon. The exact mechanism responsible for the lag phenomenon is still not fully understood.[122,125,174] Its occurrence may be related to the appearance of lower peripheral vascular resistance caused by relaxation of endothelial smooth muscle.[174] In this regard, it was shown that p38 mitogen-activated protein kinase (p38MAPK) promotes the formation of asymmetric dimethylarginine (ADMA). The latter, in turn, can inhibit the action of nitric oxide synthase and hence the production of nitric oxide. Sodium chloride was suggested to bring about p38MAPK release and hence ADMA synthesis.[153] The consequent decrease in endothelial nitric oxide formation leads to failure of arteriolar muscle to relax. It should be noted that high ADMA concentrations have been found in plasma of patients with CKD stage 5.[154,155] In recent studies involving experimental animals with chronic renal failure, high sodium chloride intake decreased nitric oxide synthase expression in certain areas of the brain, resulting in activation of the sympathetic nervous system and hypertension.[210] In addition, there is evidence that sodium overload may cause reversal of the inhibition of Na^+, K^+-ATPase through endogenous ouabain. This step would bring about an increase in intracellular sodium and calcium concentrations, subsequently causing an increase in vascular tone and blood pressure.[211] Sodium restriction should lead to the opposite effects. The contention that sodium limitation can cause vascular relaxation is consistent with the observation that long-term dialysis

patients maintained for years on a low-salt diet have peripheral vascular resistance that is lower than that of healthy controls.[212] Thus, it is entirely possible that sodium restriction may work in ways other than that of simple ECF volume contraction.

Use of Diuretics. To promote loss of sodium and water from dialysis patients, large doses of potent loop diuretics, such as furosemide, bumetanide, or torsemide, can be administered.[213–216] However, diuretic therapy is effective only when RKF is high enough to provide daily urine output of at least 100 mL.[217] The effectiveness of this therapy may not last long,[209] possibly because of a further inevitable decline in renal function. Loop diuretics should be used with caution because of the possibility of ototoxicity.[218,219] The incidence of ototoxicity appears to be greater with furosemide and much less with bumetanide or torsemide.[213,214]

Dialysate Sodium Concentration (CPG 5.3)

High concentrations of sodium in dialysate reduce the removal of sodium during dialysis and ultrafiltration.[143,144] In the 1960s, when a dialysis treatment typically lasted 6 hours, dialysate sodium levels were in the realm of 135 mmol/L.[144] However, since the early 1970s, with the advent of shorter treatments (3 times per week for ≤4 hours per treatment), removal of the required amount of excess fluid became more difficult. To overcome this difficulty, it became necessary to increase dialysate sodium to a greater concentration (eg, to the region of ≥140 mmol/L in the 1990s).[143,220] Although increasing dialysate sodium concentration can decrease morbidity both during and between treatments, such dialysates can aggravate thirst, fluid gain, and hypertension.[143,144,220,221] Similar consequences were found in patients treated with sodium profiling, a technique that increases dialysate sodium concentration early in treatment (eg, 145 to 155 mmol/L), followed by a progressive decrease (linear, step, or logarithmic) to a lower value (eg, 135 to 140 mmol/L) at the end of dialysis.[145] It should be noted that the patient's postdialysis serum sodium concentration is a function of the time-averaged dialysate level, not the terminal level of sodium in dialysate.[222] Reviews of the large volume of literature on this topic showed that sodium profiling is of uncertain benefit.[144,145,223] Some investigators had satisfactory experiences with a dialysate sodium concentration of 138 mmol/L in a large number of patients. During these studies, the dosage of antihypertensive medications often had to be decreased or discontinued.

CONCLUSION

Use of appropriate ultrafiltration techniques, dietary sodium restriction, and lower dialysate sodium concentrations[160,224] has been instrumental in attaining a true dry weight and amelioration of hypertension in many maintenance HD patients.[133] Reembracing the time-honored and useful, yet inexpensive, tool of dietary salt restriction should serve to promote the health of HD patients. During the process of controlling ECF volume and decreasing predialysis weight, the development of hypotension during dialysis or hypertension between dialysis treatments should not be construed as a failure of volume control to normalize blood pressure. The lag phenomenon noted previously should be taken into consideration when evaluating patients with persistent hypertension.[112] To more easily

control hypertension in most dialysis patients, use of a high dialysate sodium concentration and sodium profiling should be discouraged.

Finally, application of appropriate ultrafiltration with every dialysis treatment, the incessant vigilance to target and subsequently to maintain a true dry weight (which is subject to change because of loss or gain of nonfluid body tissue), and confirmation that a patient is compliant with a sodium-restricted diet combine to demand a considerable amount of time from members of the health care team. However, to obtain favorable results, an intense, totally committed, and prolonged effort—with a high degree of motivation—is required from caregivers, as well as from the patients themselves.[112]

GUIDELINE 6. PRESERVATION OF RESIDUAL KIDNEY FUNCTION

Prospective randomized trials and observational studies have confirmed that the presence of RKF is one of the most important predictors of a patient's survival.

6.1 One should strive to preserve RKF in HD patients. (A)

6.2 Methods for preserving RKF differ among patients (see CPR 6). (B)

BACKGROUND

When HD therapy is first initiated, most patients have small and significant (but inadequate) levels of RKF, and many have normal or even high rates of urine output. This level of RKF may persist for many months and years, adding continuous solute clearance and other kidney functions to the intermittent clearances provided by dialysis treatments. The volume of urine produced each day allows more fluid intake, reducing the otherwise larger fluctuations in body fluid volumes between dialysis treatments that contribute to volume overload syndromes, hypertension, and cardiac hypertrophy. Unlike hemodialyzer clearance, RKF is subject to temporary or permanent reduction caused by numerous toxic insults that often confront patients with CKD stage 5.

RATIONALE

The impact of residual function on duration of life and QOL has been evaluated extensively in PD patients,[68,225–227] but only recently has attention been given to it in HD patients (see Table 10). [81] This difference is especially striking because the number of long-term HD patients in the United States is more than 10 times as large as the number receiving PD. Possible reasons for ignoring RKF include a lack of RKF measurements in HD patients, complacency because of confidence in the larger dose of dialysis possible with HD, previous rapid decrease in urine output after HD therapy is begun, and the added inconvenience and expense of collecting urine. Measurement of RKF in HD patients also likely was ignored because, in contrast to PD, nearly all KRT is managed for the patient by nurses and technicians. Selecting a subgroup of patients who prefer self-care (PD) also selects for willingness to perform self-measurements of RKF. There also has been concern that PD is minimally adequate; thus, RKF may play a more essential role. Earlier studies showed that RKF decreased more rapidly in patients initially treated with HD compared with continuous ambulatory PD (CAPD).[228] However, recent studies showed that RKF is preserved better in HD patients than in the past, possibly because of the use of more biocompatible membranes, discontinuation of acetate as a bicarbonate precursor, high-flux dialysis, and the earlier initiation of dialysis therapy, especially in patients with diabetes.[81,229–231] More recent studies suggest that with the use of ultrapure water to dilute concentrated dialysate, RKF decreases at a rate indistinguishable from that in CAPD patients.[232]

The protective role of RKF for preserving life and extending longevity in PD patients is well recognized[68,226,227]; previous KDOQI guidelines promoted the preservation of RKF in this population.[233] More recent data show that RKF in HD patients affords many of the same benefits, including a lower dialysis dose requirement and improved patient

Table 10: Effect of Residual Kidney Function on Mortality

Author, Year	Study design	N	Follow-up (maximum)	Applicability	Predictor	Results			Quality
						Effect Size	95% CI	P Value	
Termorshuizen, 2004[61]	Prospective	740	(4.5 yr)	↑↑↑	rKt/V per week (per increase of 1/wk)	RR=0.44	0.30, 0.65	<0.0001	●

survival.[234] The reduced need for dietary potassium and fluid restriction and reduced requirement for fluid removal during HD can enhance QOL and reduce the frequency of hospitalizations. In HD patients, the continuous nature of RKF contrasts with the intermittent schedule of dialysis, whereas for PD patients, both are nearly continuous. Evidence that includes mathematical analysis of solute kinetics and comparison of outcomes in PD versus HD patients suggests that continuous clearance is more efficient than intermittent clearance.[235] Such arguments have been used, for example, to explain the much lower weekly dialysis clearance requirement in PD compared with HD patients despite nearly equal outcomes, especially in the first year of treatment. If this difference in efficiency is accepted, the contribution of RKF to overall kidney plus dialyzer function is greater than the simple addition of time-averaged clearances would suggest.

Because it appears that RKF can be preserved, every effort should be made to protect existing renal function in HD patients, especially if daily urine volume exceeds 100 mL. When measures are taken to protect RKF after initiation of HD therapy, patients may continue to experience long-term benefits, even at very low GFRs.

Suggested methods to protect RKF are detailed in CPR 6.

LIMITATIONS

Data that support reducing the dose of dialysis in patients with significant residual function are all observational. The recent randomized trial of HD dose[1] intentionally excluded patients with significant residual function; therefore, little dosing information for patients with RKF is available. It is possible that patients with residual function can derive more benefit from doses of dialysis targeted for anephric patients compared with the downward adjusted dose; therefore, a firm recommendation to reduce the dose is not possible at this time.

In rare cases, persistence of nephrotic-range proteinuria may necessitate renal embolization or removal of the kidneys. Occasionally, renal endocrine function (eg, renin secretion) contributes to hypertension, necessitating ablation or removal of the native kidneys. This scenario is much less common today compared with 40 years ago because potent antihypertensive agents are readily available. Occasionally, removal of residual kidney mass may be required to manage bacterial pyelonephritis. Before transplantation, removal of obstructed kidneys or kidneys with stones or cysts causing infections that cannot be completely eradicated with antibiotics may be warranted. In these cases, careful timing of the transplantation and nephrectomy can maximize benefit from RKF while also reducing the risk of transplantation. In some cases, removal of a transplanted kidney is warranted to eliminate symptomatic inflammation caused by continued allograft rejection.

GUIDELINE 7. QUALITY IMPROVEMENT PROGRAMS

The continuous quality improvement (CQI) process has been shown to improve clinical outcomes in many disciplines, including CKD. It presently is conducted at both the facility level and local network level.

7.1 For HD adequacy, each dialysis clinic should continue to monitor the processes related to the delivery of dialysis, such as Kt/V, reuse standards, etc. (A)

7.2 Consideration should be given to providing resources and training for expanding the assessment of clinical outcomes beyond mortality to include hospitalization rates, QOL, patient satisfaction, and transplantation rates, recognizing that without adequate resources and training, these outcomes are unlikely to be valid, and the efforts to collect such information may adversely affect patient care. (B)

7.3 Quality improvement programs should include representatives of all disciplines involved in the care of HD patients, including physicians, physician assistants, nurse practitioners, nurses, social workers, dietitians, and administrative staff. (B)

BACKGROUND

The CQI process has been shown to improve process and clinical outcomes in many disciplines, including CKD and particularly CKD stage 5.[236]

Improvement in both QOL and longevity are goals of Healthy People 2010, the strategic plan for the nation's health (www.healthypeople.gov; accessed May 1, 2006).[236A] Kidney disease is 1 of 18 focus areas for Healthy People 2010. For patients with CKD stage 5 receiving dialysis therapy, the ongoing process to improve clinical outcomes is linked inextricably to the assessment of dialysis adequacy, and the need for programs to continuously assess and improve care remains as great as ever.[237]

RATIONALE

With regard to HD adequacy guidelines, data from the HEMO Study support a plateau at the level of the existing recommended HD adequacy targets for the current practice of thrice-weekly treatments. There is no compelling evidence that additional increases in dialysis dose within the presently recommended range improve such clinical outcomes as patient mortality, hospitalization rates, QOL, patient satisfaction, and/or transplantation rates.[1] However, as the global care for dialysis patients evolves, it is reasonable to assume that so may the most effective thresholds for delivery of dialysis. Therefore, continuing monitoring of outcomes—including not only delivered dose of dialysis, but also other key aspects of established and emerging factors that impact on both QOL and longevity of life for dialysis patients—will be critical for the continuing improvement of care for the dialysis patient.

Domains of clinical outcomes to be monitored (in addition to mortality) when sufficient resources exist and validated standards have been created might include:

- Hospitalization rates
- QOL
- Patient satisfaction
- Transplantation rates

Key to this process is the commitment to an evidence-based approach that will build upon, and not detract from, the existing limited resources.[237] This would contribute to the creation of a system in which clinical outcome trends could be tracked and then meaningfully compared with regional outcome data (eg, from the CKD Stage 5 Network), national data, international data, and historical data from the facility itself. These findings could build upon the existing evidence-based recommendations for PD and HD, anemia management, and vascular access.

Comparison with regional or national data may be difficult because of limitations in adjusting for the case-mix of patients at individual centers and variations in quality of data collection to capture the adequate case-mix description. Thus, facilities that have fewer resources and less trained staff and/or more linguistically diverse patient populations are more likely to be unable to capture a complete clinical profile and more likely to underestimate case-mix severity, providing an overestimate of adjusted mortality or hospitalization rates.

For the overall care of dialysis patients, there likely will be value in tracking selected associated clinical outcomes to assess the role of HD, such as those related to reuse systems and frequent dialysis strategies. Many investigators and facilities already assess the former (eg, mortality) and the NIH is assessing the latter in a prospective study (www.clinicaltrials.gov/show/NCT00264758; accessed May 1, 2006).[237A–239] The establishment of highly functional systems and well-trained dedicated staff (including those listed next) to ensure the quality and uniformity of data collection, as well as the ability to extract which component(s) contribute to clinical outcomes, will be critical to this process.

Quality improvement program representatives should include:

- Physicians
- Physician assistants
- Nurse practitioners
- Nurses
- Social workers
- Dietitians
- Administrative staff

Hospitalization Rates

The large number of patients hospitalized at multiple facilities creates a tremendous task in the collection of accurate and valid data. Moreover, differences in similar procedures performed in an inpatient and outpatient setting vary geographically and across health

care systems. This information would need to be clarified and/or appropriately adjusted to capture meaningful data.

Quality of Life

One of the more commonly used tools to assess health-related QOL (HRQOL) for patients with CKD stage 5 is the Kidney Disease and Quality of Life Short Form™ (KDQOL-SF).[240] There is evidence that the physical, psychological, and/or mental components of HRQOL predict death and hospitalization among HD patients.[32,241–243] Unfortunately, the area of QOL assessment is still limited by the use of multiple tools, challenging attempts at maintaining uniformity in QOL data collection. Although the KDQOL-SF has been translated and used in culturally, geographically, and linguistically diverse populations, it does not appear to have been validated in these settings. This is critical because there may be significant sex, generational, and/or racial/ethnic variations in perceived—and therefore, reported—QOL.[244–247] In addition, many of the interventions shown to improve QOL have not been validated simultaneously to decrease the risk for adverse clinical outcomes.

Patient Satisfaction

Multiple factors influence patient satisfaction. Specific to HD, one key factor influencing patient satisfaction, time on dialysis therapy, is related inversely to achieving a higher dose of dialysis, higher phosphate clearance, less rapid volume removal, and other factors linked to improved clinical outcomes. This may place facilities in the situation in which patient satisfaction and clinical outcomes are in conflict, and there are no national standards for arbitrating this situation.[248]

Similar to QOL assessments, there also are multiple tools actively being used for assessing patient satisfaction that vary across and even within facilities. Without standard tools and validation of the tools, the utility of such surveys at present is insufficient to meet a clinical guideline standard. However, the continuing development and refinement of these tools is crucial to the continued improvement of care and the foundation of future guidelines.

Transplantation Rates

There are no data linking the delivery of dialysis doses within the recommended range to renal transplantation. Multiple factors influence transplantation rates, including, but not limited to, case-mix, geography, insurance status, and patient and provider bias.[249,250] While the monitoring of trends is valuable, assessment of the impact of these factors needs to be isolated, standardized, and validated into an appropriate analytical model before including dialysis transition rates to renal transplantation as a potential standard.

LIMITATIONS

These guidelines for achieving the broad clinical outcome goals of improved QOL and enhanced longevity are a summation of ongoing "best practices" that supplement the existing KDOQI HD Guidelines. These best practices and the robust evidence required to support the rigor of a CPG are still evolving. This will require a methodologically sound foundation with standards that are generalizable. Future data collection will require

assessments using prespecified approaches to data analysis that include all these factors and other related confounders (eg, demographics, case-mix, and medical therapeutics) into a clinically valid multivariable statistical model. Otherwise, the ability to ascertain the evidence of the contribution of existing clinical outcome best practices versus the achievement of recommended guidelines becomes a statistical/logistical impossibility. Such a consideration is an intense undertaking and should not be initiated without total commitment to the resources needed to address each of these issues and create the valid models needed to monitor improved care in a meaningful way. If this is not done, interpretation of partially collected or invalid data would: (1) be unable to determine the root cause of changes in clinical outcomes, (2) not be valid across and/or within facilities, and (3) add limited value above the present outcome analyses.

GUIDELINE 8. PEDIATRIC HEMODIALYSIS PRESCRIPTION AND ADEQUACY

8.1 Initiation of HD:

8.1.1 Dialysis initiation considerations for the pediatric patient should follow the adult patient guideline of a GFR less than 15 mL/min/1.73 m^2. (A)

8.1.2 For pediatric patients, GFR can be estimated by using either a timed urine collection or the Schwartz formula. (A)

8.1.3 Dialysis therapy initiation should be considered at higher estimated GFRs when the patient's clinical course is complicated by the presence of the signs and symptoms listed in Table 11, CPR 1 for adult patients, as well as malnutrition or growth failure for pediatric patients. Before dialysis is undertaken, these conditions should be shown to be refractory to medication and/or dietary management. (A)

8.2 Measurement of HD adequacy:

8.2.1 spKt/V, calculated by either formal urea kinetic modeling or the second-generation natural logarithm formula, should be used for month-to-month assessment of delivered HD dose. (B)

8.2.2 Assessment of nutrition status is an essential component of HD adequacy measurement. nPCR should be measured monthly by using either formal urea kinetic modeling or algebraic approximation. (B)

8.2.3 Principles and statements regarding slow-flow methods for postdialysis sampling and inclusion of RKF (or lack thereof) outlined in the adult guidelines also pertain to pediatric patients. (B)

8.3 Prescription of adequate HD:

8.3.1 Children should receive at least the delivered dialysis dose as recommended for the adult population. (A)

8.3.2 For younger pediatric patients, prescription of higher dialysis doses and higher protein intakes at 150% of the recommended nutrient intake for age may be important. (B)

8.4 Non–dose-related components of adequacy:

Accurate assessment of patient intravascular volume during the HD treatment should be provided to optimize ultrafiltration. (B)

BACKGROUND

Provision of evidence-based pediatric HD adequacy guidelines is hampered by a number of epidemiological issues. Stage 5 CKD remains a relatively uncommon disease, and renal transplantation is still the predominant and preferred KRT modality for children. In addition, PD is a viable modality option for many pediatric patients. Finally, children with CKD stage 5 show significantly better survival rates compared with adult patients. As a result of these factors, no long-term pediatric outcome study comparable to the HEMO Study or the National Cooperative Dialysis Study (NCDS) would be adequately powered

to detect an effect of delivered HD dose on pediatric patient outcome. Nevertheless, some recent pediatric data exist to describe the most accurate methods for quantifying urea removal, correlate delivered dose of dialysis with inflammation, and examine other components of the dialysis prescription, including ultrafiltration and nutrition provision. These data can serve as the basis for CPRs in caring for children receiving HD. For areas in which no pediatric data exist, CPGs and CPRs for adult patients should serve as a minimum standard for pediatric patients.

RATIONALE

Although the Schwartz formula overestimates GFR, especially at lower GFR levels, recent pediatric data show that GFR estimated by using the Schwartz formula of 15 mL/min/1.73 m^2 or less had excellent negative predictive value for a measured GFR of 20 mL/min/1.73 m^2 by iothalamate clearance.[21,251] Because 24-hour urine collections often are not possible for smaller non–toilet-trained children, reliance on serum creatinine–based formulas is essential in this subset. As with the MDRD equation, use of the Schwartz formula is simple and does not depend upon collection of urine samples. The Schwartz formula contains a cofactor that accounts for patient sex and age to incorporate estimates of lean muscle mass.

Modality choice is governed by a number of factors, including patient size, availability of a caregiver to competently perform home dialysis, and the expected length of waiting time for a renal allograft. Children weighing less than 10 kg are better suited for PD because HD in very small children requires extensive nursing expertise. Also, because infants require greater nutritional needs to promote growth on a per-kilogram basis, thrice-weekly HD often is insufficient to maintain acceptable fluid, potassium, and electrolyte balances. HD should be strongly considered for patients who do not have one, and preferably two, caregivers who are competent and motivated to provide home PD. For patients who have a consenting living renal allograft donor available and who have substantial urine output and electrolyte control, initiation of maintenance dialysis therapy may be avoided if a preemptive transplantation can be scheduled expeditiously.

Monthly solute clearance and nutrition status measurement using urea as the surrogate small molecule are essential to assess the dose of dialysis in pediatric patients because patients receiving optimal dialysis should grow and gain weight through adolescence. Thus, assessment of Kt/V will guide the practitioner to increase dialyzer size, blood flow rates, or dialysis treatment time as patients grow. Single-center pediatric data exist that show the Daugirdas formula reliably estimates spKt/V derived by using formal urea kinetic modeling.[252] An essential component of adequacy measurement is nutrition status assessment because recent pediatric data show that increased delivered dialysis dose does not in and of itself lead to improved nutritional intake.[253] Pediatric data show that nPCR is more sensitive than serum albumin concentration as a marker of protein-energy malnutrition in a small group of malnourished children receiving HD.[254,255]

No large-scale studies exist to validate a target spKt/V or eKt/V as adequate for the pediatric HD population, although methods for accurate measurement of each have been validated in children.[254,256] Certainly, because infants and young children have greater

nutritional requirements to support growth, pediatric patients should receive at least the minimum dialysis dose as prescribed for adults. A study showed that pediatric patients who receive a thrice-weekly Kt/V of 2.0 and 150% of the recommended daily allowance of protein were able to show catch-up linear growth without the use of recombinant growth hormone.[257] Chronic inflammatory mediator levels seem to be inversely proportional to eKt/V in pediatric HD patients,[258] although an optimal eKt/V level has not been established to mitigate chronic inflammation, which is related in large part to dialysis vintage. Thus, a case can be made for providing pediatric patients with a Kt/V greater than the adult-based guideline of 1.2, but a larger scale study is warranted to determine an optimal Kt/V target. Such a strategy will ensure that smaller growing pediatric patients receive enough nutrition and adequate waste product clearance. Observational pediatric data exist showing that older, larger, and African-American children are less likely to receive an spKt/V greater than 1.2 consistently[259]; therefore, practitioners should be informed to make specific efforts to ensure the provision of adequate dialysis in these vulnerable populations.

Management of pediatric HD patient fluid status is especially difficult because children are expected to grow and gain weight from infancy through adolescence. Thus, distinguishing between real weight accretion versus fluid overload is critical to prevent a chronic fluid-overloaded state that can lead to chronic hypertension and resultant CVD. Given the relative high ultrafiltration rate to dialysis treatment time ratio and the relative inability of younger patients to accurately verbalize symptoms from overly rapid ultrafiltration, the means to accurately assess patient intravascular volume can help optimize ultrafiltration to attain patient true target dry weight while minimizing intradialytic symptoms. Noninvasive monitoring (NIVM) of hematocrit during the dialysis treatment uses an in-line sensor to reflect the change in patient blood volume as an inverse change in patient hematocrit during fluid removal. Ultrafiltration guided by NIVM algorithms that adjust UFRs and targets based on hourly NIVM blood volume changes have been shown to decrease patient symptoms, hospitalization, extra treatments for fluid overload and hypertension, antihypertensive medication requirements, and fourth weekly HD treatments for pediatric patients receiving HD.[260–262]

LIMITATIONS

Any pediatric study to determine either an adequate or optimal delivered dialysis dose requires practical end points to be valid. Whereas death and hospitalization rates are easily measurable end points, their relative infrequency in the pediatric HD population and the low prevalence of pediatric CKD stage 5 make an adequately powered study using these end points a virtual impossibility.

II. Clinical Practice Recommendations for Hemodialysis Adequacy

CLINICAL PRACTICE RECOMMENDATION FOR GUIDELINE 1: INITIATION OF DIALYSIS

Certain complications of kidney failure justify initiation of dialysis treatment in patients for whom estimated GFR has not yet decreased to 15 mL/min/1.73 m^2 (Table 11).

Table 11. Complications That May Prompt Initiation of Kidney Replacement Therapy

Intractable ECV overload
Hyperkalemia
Metabolic acidosis
Hyperphosphatemia
Hypercalcemia or hypocalcemia
Anemia
Neurological dysfunction (eg, neuropathy, encephalopathy)
Pleuritis or pericarditis
Otherwise unexplained decline in functioning or well-being
Gastrointestinal dysfunction (eg, nausea, vomiting, diarrhea, gastroduodenitis)
Weight loss or other evidence of malnutrition
Hypertension

CLINICAL PRACTICE RECOMMENDATIONS FOR GUIDELINE 2: METHODS FOR MEASURING AND EXPRESSING THE HEMODIALYSIS DOSE

For patients managed with HD, both dialyzer and native kidney function can be measured periodically to assess the adequacy of replacement therapy. Urea clearance is the preferred measure of both (see Guideline 2).

- **2.1 Residual kidney urea clearance (Kr) is measured best from a timed urine collection.**
- **2.2 For purposes of quality assurance, the delivered dose should be measured and compared with the prescribed dose each month.**

BACKGROUND

Failure to include K_r in the model of urea kinetics will not harm the patient provided the dose of dialysis is adequate. Inclusion of K_r is advantageous because it allows accurate measurement of G and nPCR (or nPNA), which otherwise are underestimated in patients with significant RKF and are helpful to assess dietary adequacy. Inclusion of K_r also allows a potential reduction in the duration and frequency of dialysis as a means of improving QOL by extending time off dialysis. Limiting time and reducing the intensity of dialysis may benefit some more than others, depending on lifestyle and treatment tolerance. Mathematical analysis of solute kinetics during and between HD treatments shows that average and peak solute levels are controlled better by continuous (compared with intermittent) clearance, and that increasing the frequency of a given weekly clearance also lowers levels of dialyzable solutes. Comparison of delivered dose with prescribed dose of dialysis adds another dimension to the analysis of adequacy that can spot problems with the blood access device and dialysis equipment, including blood and dialysate pumps. This function is independent of the determination of adequacy.

RATIONALE

Adding RKF to Dialyzer Clearance

If K_r is included in the dialysis prescription, it becomes important to measure K_r frequently to avoid prolonged periods of underdialysis as K_r is lost. The rate of loss may vary among patients. In some patients, monthly measurements are advised, whereas in others with good urine output, quarterly measurements will suffice. If infrequent measurements are chosen, the patient and dialysis staff must be alert to changes in urine output and exposure to toxic insults (see Table 16, CPR 6). Urine output roughly correlates with RKF, but it should not be used as the sole determinant because it does not predict RKF accurately in individual patients.[81] Patients with potentially recoverable renal function represent a special group in whom regular measurements of RKF are especially advantageous. Failure to follow up RKF closely may lead to unnecessary prolongation or perpetuation of dialysis in a patient with adequate native kidney function who does not require dialysis.

For both PD and HD, the preferred measure of RKF is urea clearance. This differs from recommended measures of kidney function in patients with CKD stages 1 to 4, for whom

creatinine clearance has been the traditional index, as well as the serum creatinine–based estimate of GFR derived from the MDRD Study.[263] Reasons for recommending urea clearance as opposed to other techniques include the following:

- Unlike creatinine clearances, measurements of urea clearance are not confounded by renal tubular secretion.
- Native kidney urea clearances are lower than the kidney's GFR, so the patient is protected. Conversely, creatinine clearances are always higher than GFR.
- MDRD estimates of GFR based on serum creatinine level are not valid in patients managed with dialysis.
- Inclusion of native kidney urea clearances in kinetic modeling programs allows accurate calculation of G and nPCR as an aid to diet assessment.

When K_r is included in the expression of overall excretory function, the method for combining intermittent dialyzer clearance with continuous K_r requires some effort. Methods for adding K_r to K_d should take into account the additional clearance that RKF provides between dialysis treatments and the increased efficiency of continuous (compared with intermittent) clearance. Suggested methods for combining K_r with K_d can be found in Appendix. Caution must be exercised when using any of the methods found in the Appendix to adjust the dialysis dose for K_r values above 2 mL/min. Other potentially vital benefits of dialysis must be considered when contemplating a reduction in dose based solely on urea kinetics. An alternative simplified method (using a table) for adjusting spKt/V in patients with Kr $>$ 2 mL/min/1.73 m^2 can be found in CPR 4, *Minimally Adequate Hemodialysis.*

It is important to note that the adequacy standards described in these guidelines and CPRs that refer to dialysis-session-based spKt/V values do not include an adjustment for the continuous component of residual urea clearance.

One of the disadvantages of adjusting the HD dose according to RKF is the patient's perception of worsening health when the ultimate decrease in native kidney function requires longer treatment times. Successive prolongations of dialysis can contribute to psychological depression that further compromises the patient's QOL and, possibly, survival.[32] Incremental dosing while counseling the patient to anticipate the increase in treatment time as renal function is lost is the Work Group's preferred approach.

How to Measure More Frequent Dialysis

The correction for rebound at the end of dialysis (see previous discussion of eKt/V) reduces, but does not eliminate, the effect of intermittence and disequilibrium on dialysis efficiency. Efficiency is defined as the effect of lowering solute concentration achieved for a given level of dialysis dose. Because the dose is defined as a clearance, the solute level is inversely proportional to the dose and the relationship between the 2 is curvilinear, eventually reaching a plateau of effectiveness as dialysis dose is increased. Intermittent dialysis therefore, in contrast to continuous dialysis, has a self-limiting aspect that diminishes its efficiency. If the efficiency of continuous dialysis is defined as unity, then the efficiency of thrice-weekly dialysis has been estimated as 0.7 or less, depending on

the solute. The greater the solute disequilibrium, the lower the efficiency of intermittent dialysis. Increasing the frequency, ie, moving toward a more continuous pattern, increases efficiency. An adjustment in dose therefore theoretically is necessary to account for the improvement in efficiency for dialysis schedules that are more frequent than 3 times per week. This concept is inherent in the already accepted dictum that the same weekly dose given once or twice weekly will not suffice to maintain HD adequacy.

The recommended method for normalizing and expressing the dose of dialysis independent of frequency is to reduce the expressed delivered dose to a continuous equivalent clearance.[202,264,265] This method relies on calculated average or peak concentrations of the index solute and assumes a weekly steady state of generation and removal. Under such conditions, the solute removal rate will equal the generation rate. In addition, the well-known relationship between clearance and concentration dictates that the average solute level will be proportional to the generation rate and inversely proportional to the continuous equivalent clearance (K_{ce}):

$$C_{av} = G/K_{ce}$$

$$K_{ce} = G/C_{av}$$

where C_{av} is average concentration

The value of K_{ce} for urea is calculated easily by using formal urea modeling that produces both G and time-averaged C (TAC).[264] However, the resulting clearance is significantly higher than a consensus-derived continuous equivalent clearance for PD. This observation led 2 groups to propose using the average peak or average predialysis urea concentrations as the target instead of mean concentration.[265,266] This substitution of a higher concentration than C_{av} in the expressions resulted in a lower average clearance, more in keeping with the accepted continuous peritoneal clearances for CAPD. The resulting quasiclearance was called "standard K" and "standard Kt/V" (stdKt/V).[265] Another proposed approach is to model the kinetics of other solutes because almost all other small and large dialyzable solutes have greater disequilibrium than urea.[267,268] As noted, the inefficiency of intermittent dialysis is accentuated by disequilibrium. All these methods produced a set of curves relating spKt/V to stdKt/V or normalized Kt/V that were similar, partially because parameters were chosen in each case to "force" the resulting continuous equivalent clearance to match the accepted values for continuous PD (CAPD). stdKt/V is calculated easily by using formal urea kinetic modeling and has been chosen by the NIH-sponsored Frequent HD Network as the frequency-normalized expression to monitor dialysis doses in their study of daily HD outcomes.

Conversion of spKt/V to stdKt/V can be approximated by using an explicit equation that assumes a symmetric weekly schedule of dialyses, no K_r, and a fixed volume (V).

This method was presented first by Gotch in 1998 and later refined by Leypoldt in 2004[71]:

$$_{std}Kt/V = \frac{10080\,\frac{1-e^{-eKt/V}}{t}}{\frac{1-e^{-eKt/V}}{_{sp}Kt/V} + \frac{10080}{Nt} - 1}$$

where N is number of treatments per week and eKt/V is derived from spKt/V by using 1 of the expressions in Table 4. It should be noted that stdKt/V calculated using this equation may differ slightly from stdKt/V calculated using the more exact method described previously that takes into account other variables, such as ECF volume expansion/contraction, asymmetry of the weekly schedule, and K_r.

The complexities of normalizing more frequent HD to a continuous equivalent clearance perhaps have contributed to a lack of consensus about dose expressions for the increasingly popular schedule of 4 treatments per week. The extra dialysis treatment often helps with management of larger patients, patients with refractory anemia, and patients with excessive fluid gains. Most of these methods require formal kinetic modeling and modeling programs that are not locked into 3 treatments per week. In addition, regulatory agencies have not caught up with these concepts and continue to demand a minimum Kt/V of 1.2 per dialysis as if they are given 3 times per week. If an extra dialysis treatment is given, a simple mathematical calculation shows that the minimum dose per dialysis required if the minimum for 3 times per week is 1.2 per dialysis is 0.9 per dialysis to achieve the same weekly clearance. This calculation assumes that all dialysis treatments are equal and the extra treatment produces no gain in efficiency. This conservative calculation will provide more dialysis for the patient than is apparent from the expressed dose, which effectively protects the patient from underdialysis. Alternatively, the dialysis clinic can simply multiply the measured Kt/V by 4 and divide by 3 to obtain the equivalent of Kt/V for 3 treatments per week.

Quality Assurance

The Work Group continues to recommend comparisons of prescribed with delivered doses as a quality assurance aid. Guideline 4 provides a minimum Kt/V threshold below which action should be taken to prevent underdialysis. However, even if the dose is adequate, comparison of prescribed with delivered dose has potential additional benefit for the patient. If significantly different (>15% difference), troubleshooting should be done to detect other problems that may impact on future dosing, such as AR or a faulty blood pump. In practice, comparison of prescribed with delivered dose is accomplished by comparing modeled V with real V. The latter is determined preferably by averaging previous values of modeled V, but also can be determined by using an anthropometric formula, eg, Watson.[269] If a problem exists with delivery, usually modeled V is significantly

greater than real V. Because urea modeling provides a ratio of K/V, the inflated V is caused by an inordinately high prescribed K compared with delivered K. Prescribed K is determined from the dialyzer specification, K_0A, and flow rates, whereas modeled K/V is determined mainly from changes in BUN levels during the dialysis. Comparison of modeled V with a previously determined patient-specific value for V is equivalent to comparing delivered with prescribed clearance. When V is too high, efforts should be made to detect such problems as AR, an error in dialysis timing, inadequate blood pump occlusion or calibration, faulty dialysate pump, error in blood sampling, or inadequate performance of the dialyzer (eg, because of clotting during dialysis or excessive reuse).

4.1 High-Flux Membrane:
When methods to achieve good dialysate water quality are available, high-flux HD membranes should be used, defined as those providing β_2-microglobulin (β2M) clearance of at least 20 mL/min under conditions of actual use.

4.2 Minimum dose with hemofiltration or hemodiafiltration:
The recommended minimum delivered dose target, measured by using pretreatment and posttreatment BUN levels, is the same as that for HD.

4.3 Minimum spKt/V levels for different dialysis schedules:

4.3.1 Two to 6 treatments per week are appropriate for certain patients.

4.3.2 Twice-weekly HD is not appropriate for patients with K_r less than 2 mL/min/1.73 m^2.

4.3.3 Minimum spKt/V targets for 2-, 4-, and 6-times-per-week dialysis schedules logically should be different from that for the thrice-weekly schedule. In the absence of dose-ranging outcomes data, minimum spKt/V targets for different schedules can be based on achieving a minimum stdKt/V of 2.0 per week.

4.3.4 The target spKt/V dose should be at least 15% higher than the listed minimum dose because of the variability in measuring Kt/V, as discussed in Guideline 4.

4.4 RKF (measured by Kr):

4.4.1 The minimally adequate dose of dialysis can be reduced in patients with K_r greater than 2 mL/min/1.73 m^2.

4.4.2 In the absence of dose-ranging outcomes data, the minimum spKt/V target for patients with substantial RKF can be reduced, but the reduced target should be no lower than 60% of the minimum target for patients with no residual renal function (the reduction depends on dialysis frequency), per values provided in Table 13.

4.4.3 When the minimally adequate dose is reduced because of substantial RKF, K_r should be monitored at least quarterly and as soon as possible after any event that might have acutely reduced RKF.

4.5 Increase in minimally adequate dose for women and smaller patients:
An increase in the minimally adequate dose of dialysis should be considered for the following groups of patients:

4.5.1 Women of any body size.

4.5.2 Smaller patients, for example, patients with values for anthropometric or modeled V of 25 L or lower.

4.6 Dialysis adequacy for patients who are malnourished and/or losing weight:

An increase in the minimally adequate dose of dialysis and/or a change to a more frequent dialysis schedule should be considered for the following groups of patients:

4.6.1 Patients whose weights are 20% less or lower than their peer body weights.

4.6.2 Patients with recent otherwise unexplained and unplanned weight loss.

4.7 Dialysis adequacy for patients with hyperphosphatemia or chronic fluid overload and other categories of patients who might benefit from more frequent dialysis:

A change to a more frequent dialysis schedule should be considered for the following groups of patients:

4.7.1 Patients with hyperphosphatemia.

4.7.2 Patients with chronic fluid overload with or without refractory hypertension.

4.8 A change to a more frequent dialysis schedule may be beneficial to a broader group of patients in terms of improving QOL and quality of sleep, reducing sleep apnea, and improving sensitivity to erythropoietin.

4.9 Minimum dialysis treatment time for thrice-weekly schedules:

The minimum HD treatment time for thrice-weekly dialysis in patients with K_r less than 2 mL/min should be at least 3 hours.

RATIONALE

High-Flux Membrane (CPR 4.1)

The β2M molecule has an important role in the pathogenesis of dialysis-related amyloidosis, which is seen primarily in HD patients who have been dialysis dependent for more than 5 years. An important question is whether use of membranes that clear β2M gives rise to superior outcomes over shorter periods, especially in terms of such hard outcomes as mortality and hospitalization. The primary results of the HEMO Study suggested that assignment to dialysis using a high-flux membrane had no significant effect on patient mortality or a variety of main secondary outcomes that combined mortality with either hospitalization or decrease in serum albumin levels.[1] However, in contrast to results of dose randomization (for which the mean effect size of dose on mortality or secondary outcomes was close to zero) in the flux analyses, the mean effect size for mortality, as well as for several of the secondary outcomes, was fairly consistently close to a 10% benefit, although the 95% confidence intervals (CIs) included zero. Further analysis of the HEMO Study data showed that assignment to high-flux dialysis improved mortality (as well as main secondary outcomes) in higher vintage patients, ie, those dialyzed longer than the median time of 3.7 years at baseline.[270] This analysis in higher vintage patients

was predefined at the outset of the HEMO Study before beginning the trial. Furthermore, some of the secondary outcomes—in particular, composites focusing on cardiovascular death and/or cardiovascular hospitalizations—were improved in the group assigned to high-flux therapy.[271]

During the KDOQI HD update period, 2000 to 2005, no other randomized trials assessing hard end points (mortality and/or hospitalization) in patients undergoing high-flux versus low-flux dialysis were published. Several randomized trials looked at the effects of high-flux dialysis on predialysis β2M levels, and all found a measurable effect (reduction in level with high-flux dialysis), including the HEMO Study (see Table 12). [270,272,273]

Additional observational studies suggested that the mortality rate might be decreased in patients dialyzing with high-flux membranes (see Leypoldt, 1999,[274] and Woods, 2000[275] in Table 12). After results of the HEMO Study were disclosed, analysis of mortality versus flux data from the 1999 to 2000 USRDS, published in abstract form, found a small mortality risk reduction (relative risk [RR], 0.972; 95% CI, 0.950 to 0.995) in prevalent patients, and an RR of 0.951 (CI, 0.937 to 0.966) in incident patients dialyzed with high-flux membranes.[277A] However, this abstract has not been published as an article in a peer-reviewed journal.

In a large European cohort of patients making up the Lombardi registry, mortality and risk for carpal tunnel surgery were compared in patients undergoing (mostly low-flux) HD, hemodiafiltration, and hemofiltration.[278] A 10% mortality risk reduction was found in patients treated with either hemodiafiltration or hemofiltration compared with mostly low-flux HD, but the CI included zero. However, the investigators found a significant risk reduction for carpal tunnel surgery in the hemodiafiltration/hemofiltration groups.

The most recent European Best Practice Guidelines include recommendations for the use of high-flux membranes, supported by level B evidence (Guideline II.2.1) and also recommend the addition of a convective component to enhance middle-molecule removal, also with level B evidence (Guideline II.2.2).[279] However, a recent Cochrane group review, looking at a meta-analysis of RCTs studying the effect of dialysis membrane on outcome, concluded that it was too soon to make a definitive recommendation.[273]

The Work Group ultimately decided that the evidence for benefits of high-flux membrane use in terms of hard outcomes was suggestive, but not definitive enough to be formulated as a guideline, taking a more conservative approach than the European group. However, the Work Group decided that the evidence for mortality reduction was strong enough for a CPR encouraging high-flux dialysis. The evidence is incontrovertible that high-flux dialysis decreases predialysis serum β2M levels (Table 12),[270,272,273] and lower predialysis β2M levels were linked to improved outcome. Furthermore, reduced long-term consequences of β_2-amyloidosis with the use of high-flux membranes was reported by 2 groups,[280,281] confirming a much earlier report.[282]

The Work Group also specified a definition of high-flux dialysis. In the HEMO Study, β2M clearances were measured in vivo, and a clearance of at least 20 mL/min was defined as adequate for a dialyzer to be considered high flux (the low-flux dialyzers used had β2M clearance indistinguishable from zero). Because the manufacturing industry has learned how to expand β2M clearances while minimizing albumin leakage, current dialyzers are

Table 12: Effect of High Flux Dialysis on Mortality, Cardiovascular Mortality and β2 Microglobulin (β2M)

Author, Year	Study design	N	Follow-up (maximum)	Applicability	Predictor	Outcome	Results			Quality
							Effect Size	95% CI	P Value	
Mortality										
Cheung, 2003[270]	RCT	All: 1846	(6.6 yr)	↑↑↑	High Flux vs. Low Flux	Mortality	RR=0.92	0.81, 1.05	NS	●
		≤3.7 yr on dialysis: 1269					RR=1.05	0.89, 1.24	NS	
		>3.7 yr on dialysis: 577					RR=0.68	0.53, 0.86	0.001	
MacLeod, 2001[273]	Meta-analysis (32 studies)[a]	438	nd	↑↑	Synthetic vs. cellulose/modified cellulose HD membranes	Mortality	OR=1.20	0.61, 2.37	NS	⊙
Leypoldt, 1999[274]	Retrospective cohort	1771	nd	↑↑	K_{eff}/V (per 10% increase)	Mortality	RR=0.95		<0.0001	○
Woods, 2000[275]	Retrospective cohort	All: 715	(5 yr)	↑	High Flux vs. Low Flux	Mortality	nd		NS	○
		Non-diabetic: 644					HR=0.37	0.15, 0.84	0.02	
Cardiovascular Mortality										
Cheung, 2003[270]	RCT	All: 1846	(6.6 yr)	↑↑↑	High Flux vs. Low Flux	Cardiovascular mortality	RR=0.80	0.65, 0.99	0.04	●
		≤3.7 yr on dialysis: 1269					RR=0.91	0.70, 1.18	NS	
		>3.7 yr on dialysis:577					RR=0.63	0.43, 0.92	0.02	
β2 Microglobulin										
Cheung, 2003[270]	RCT	1846	(6.6 yr)	↑↑↑	High Flux vs. Low Flux	β_2M	33.6 vs. 41.5		<0.0001	●
Locatelli, 2000[272]	RCT	84	(12 wk)	↑↑	High Flux vs. Low Flux	Δ in median pre-dialysis β_2M (mg/L)	-6.4 vs. +0.7		0.004[a]	●
						Δ in median post-dialysis β_2M (mg/L)	-4.0 vs. +2.1		0.002[a]	
MacLeod, 2001[273]	Meta-analysis (32 studies)[b]	407	nd	↑↑	Synthetic vs. Cellulose/modified cellulose HD membranes	Pre-dialysis β_2M (mean difference)	-13.82	-16.95, -10.69	<0.05	⊙
Schiffl, 2000[276]	Retrospective cohort	89	nd	↑	High flux vs. Low Flux	β_2M -Amyloidosis	OR=0.28	0.12, 0.65	0.003	○

a Univariate analysis
b Studies in meta-analysis are not replicated in table.

available with much greater β2M clearances, and the clearance can be increased still further by the use of hemodiafiltration and/or novel dialyzer designs. The value of 20 mL/min was adopted for these guidelines because it corresponded to the minimum level obtained in the HEMO Study, which provided much of the evidence for this CPR.

Minimum Dose With Hemofiltration or Hemodiafiltration (CPR 4.2)

Urea is a surrogate adequacy molecule for measuring clearance of a large family of uremic toxins, some of which may have a much higher molecular weight. Because convective removal accelerates removal of larger (>5 kd), yet permeable, solutes during extracorporeal therapy, it might be argued that with hemofiltration, the ratio of removal of these larger molecular-weight toxins to urea removal is higher; hence, minimal adequacy parameters based on urea removal either do not apply or existing minimal adequacy guidelines based on urea removal should be lower when hemofiltration is used. No dose-finding studies of hemofiltration that report hard outcomes could be identified by the Work Group. In the absence of data to the contrary, the Work Group decided to maintain recommended minimum adequacy standards for urea removal for both hemofiltration- and hemodiafiltration-based therapies. With hemodiafiltration, urea removal usually is unchanged or slightly enhanced by the supplemental filtration, so this was a somewhat moot issue. However, for some forms of primarily hemofiltration-based dialysis therapy (in which limited amounts of replacement fluid are used), the recommended minimum levels of urea removal may be difficult to achieve. The Work Group decided, on the basis of current evidence and lack of an interaction between urea-based adequacy and flux in the HEMO Study, that it would be prudent to recommend the same minimum levels of spKt/V for HD, hemofiltration, and hemodiafiltration.

Minimum spKt/V Levels for Different Dialysis Schedules (CPR 4.3)

The KDOQI 2000 HD Adequacy Guidelines gave adequacy recommendations only for thrice-weekly HD schedules. Since the last update, 1 important cross-sectional study appeared suggesting that survival in patients treated with twice-weekly HD was no worse (and was possibly better) in a USRDS patient sample.[234] Given these data and with earlier initiation of dialysis in patients with higher levels of RKF, the Work Group decided that thrice-weekly HD as a minimum frequency level was no longer appropriate. Based on solute kinetics (discussed later), the Work Group was comfortable recommending a twice-weekly dialysis schedule, but only for patients with substantial RKF.

Also, since the KDOQI 2000 update, a large set of studies was published regarding the potential advantages of giving dialysis treatments more often than 3 times per week. The number of treatments ranges from an additional fourth treatment per week in patients who have problems controlling volume[283] to offering short "daily" dialysis treatments ranging from 1.5 to 3 hours (or longer) 4 to 6 times per week. An alternative method of extending therapy is to greatly increase dialysis treatment time (from the usual 2.5 to 5 hours) to 7 to 10 hours by giving dialysis at night. Various frequency schedules for nocturnal dialysis have been reported, from 3 to 6 times per week.[284] Simple avoidance of the 2-day interdialysis interval by giving dialysis every other day also has been advocated.[285]

At the time of the present guideline update, no RCTs have been conducted to measure hard outcomes (mortality and/or hospitalization) comparing conventional thrice-weekly dialysis with either short-daily or nocturnal HD. Also, no dose-finding RCTs have appeared comparing frequent short dialysis with longer nocturnal regimens in an effort to achieve varying degrees of solute removal.

Given the lack of maturity of the research data in this field, the Work Group decided to refrain from making specific recommendations about the usefulness of these therapies in terms of a guideline or from proposing guidelines regarding minimally adequate therapy given more frequently than 3 times per week.

How to measure adequacy of more frequent therapies is not established. One of the main benefits of more frequent therapies may be ridding the body of solutes that are difficult to remove, such as phosphate, β2M, or some still unknown uremic toxins. Another benefit may be in better control of salt and water balance, which may impact on patient survival as much as solute control. In particular, the Work Group was impressed with observational data linking hard outcomes to calcium-phosphorus product,[286] as well as better control of serum phosphorus levels with more intensive daily dialysis schedules[200] and most nocturnal dialysis schedules.[284] Because 2, 4, 5, and 6 treatments per week (nocturnal and/or short-daily therapies) increasingly are prescribed, the Work Group decided that some guidance was needed in terms of minimally adequate doses.

Although an argument could be made that urea is not the only solute to use for measuring doses in a more frequent dialysis setting, control of small-solute levels in patients is vital to survival, so the Work Group decided to base recommendations for this CPR on urea. Potential alternative solutes, such as β2M, are not as clearly linked to outcome. Phosphate, while clearly linked to outcome, has complex and as yet poorly defined kinetics, and serum levels are affected not only by dialysis, but also by diet and consumption of phosphorus binders. One of the major disadvantages of urea is the rapidity of its diffusion among body compartments (high intercompartmental mass transfer area coefficient). This limitation can be minimized by using the stdKt/V construct, as described in detail in CPR 2 and in the Appendix. When the dialysis dose is expressed as stdKt/V, it seeks to control the mean pre-dialysis BUN, but, alternatively, it can be considered to model a well-cleared, but highly sequestered, solute with a low intercompartmental mass transfer area coefficient. Because highly sequestered solutes will have a large rebound after dialysis, the time-averaged blood level will be close to the mean predialysis level. stdKt/V also has the quality of reflecting advantages of a more frequent dialysis schedule that more efficiently removes sequestered solutes, such as phosphorus, but also possibly including a whole range of dialyzable solutes in the 100 to 1,000 d molecular-weight range.

In developing this CPR, the Work Group decided to target a minimum dialysis dose equivalent to an stdKt/V level of 2.0 per week. This is the level obtained when one dialyzes using a thrice-weekly schedule to an spKt/V of approximately 1.2 per treatment over 3.5 hours (Table 19).

In the absence of RKF, it is not possible to reach an stdKt/V of 2.0 by using a twice-weekly schedule. Kinetic modeling was used to examine the levels of spKt/V per treatment that would be required to reach a weekly stdKt/V value of 2.0 for twice-weekly to

Table 13. Minimum spKt/V[a] Values Corresponding to a stdKt/V[b] of Approximately 2.0 per Week

Schedule	K_r <2 mL/min/1.73 m^2	K_r >2 mL/min/1.73 m^2
2x/wk	Not recommended	2.0[c]
3x/wk	1.2	0.9
4x/wk	0.8	0.6
6x/wk (short daily)	0.5	0.4

a. Dialyzer clearance only, expressed per dialysis
b. Calculated using a 2-compartment mathematical model. Assumptions: patient with V = 35 L (should not matter); T_K is constant; K_r varies; ultrafiltration is 7 L/wk; nPCR is 1 g/kg/d (should not matter); dialyzed compartment is 1/2 of total V; K(urea) is 0 or 2 mL/min; symmetric schedule.
c. Not recommended unless Kr > 2
It is important to note that the minimum values for spKt/V shown in this table do not take into account reported improvements in outcome from increasing Kt/V when dialysis frequency is increased to more than 3x/week.

7-times-weekly schedules by using dialysis treatment times ranging from 2 to 8 hours. The simulation was performed both in the absence of RKF and when K_r was 2 mL/min. This simulation was used to arrive at the recommended minimum values in Table 13.

These spKt/V values should be considered minimum values, not target values. It is especially important to note that extending dialysis time is much more effective for controlling solute levels when frequency is increased to 4 to 7 treatments per week. Particularly in short-daily therapies, longer treatment times markedly improve phosphate removal.

From Table 19, similar spKt/V values can be determined for 8-hour treatments more typical of nocturnal HD. Usually the Kt/V for an 8-hour treatment, even at reduced dialysate and blood-flow rates, will be greater than 1.0; hence, the Work Group did not believe that adequacy determined by predialysis or postdialysis BUN monitoring is appropriate for nocturnal HD schedules.

Target spKt/V Values per Treatment for More-Frequent Therapies In contrast to thrice-weekly schedules, for which there are good data regarding the variance in Kt/V on repeated measurements, no such data have been published for short-daily dialysis, although there is no reason to assume that it would be much different from the 10% variance found in the HEMO Study. For this reason, the Work Group recommended targeting an spKt/V value that is about 15% higher than the recommended minimum targets in Table 19 in the Appendix.

Residual Kidney Function (CPR 4.4)

The KDOQI 2000 HD Adequacy Guidelines left unspecified any adequacy recommendations for patients with substantial RKF (GFR $\geq$5.0 mL/min/1.73 m^2, defined as the average of urea plus creatinine clearance). Given the trends and recommendations for earlier institution of dialysis therapy and perhaps the more successful preservation of RKF in the past several years, a large number of currently dialyzed patients have substantial RKF. A consideration of solute kinetics shows that even low levels of RKF can account for removal of large amounts of solute, including such large-molecular-weight solutes as β2M, in addition to helping maintain salt and water balance. Although there are no reliable outcome data suggesting that the delivered dose of dialysis might safely be reduced in patients with substantial RKF, reduction of the extracorporeal dose makes sense from a solute-kinetics viewpoint. The HEMO Study deliberately excluded patients with K_r for urea greater than 1.5 mL/min and hence cannot be of guidance. Observational

studies suggested a benefit of even small levels of RKF in terms of survival and other secondary outcome measures, so it is clear that all possible efforts should be expended to maintain RKF (see Guideline 6).

The Work Group was of the opinion that, at the present state of incomplete knowledge, the best way to adjust for residual renal urea clearance is to add it to the weekly stdKt/V. Residual urea clearance of 2 mL/min is approximately 20 L/wk of clearance; accordingly, in a patient with V = 30 L, it represents about a 0.67 weekly Kt/V unit. Table 13 shows spKt/V values per treatment corresponding to a weekly stdKt/V value of 2.0 in patients undergoing 2 to 6 treatments per week after adjusting (or not) for a weekly K_r of 2 mL/min. In discussing adjustments for K_r, the Work Group had 2 broad areas of concern.

First, the kinetic effect of RKF is so powerful that in patients with K_r greater than 2 mL/min, an equivalent reduction in spKt/V would result in very low recommended values. The Work Group believed this was undesirable for 2 reasons: (1) very low Kt/V values, especially for the twice-weekly or thrice-weekly schedules, would limit other potential beneficial effects of dialysis, including salt and water control; and (2) RKF sometimes can decrease precipitously. Patients who were receiving a markedly reduced dose of dialysis because of a higher K_r then might be underdialyzed for a few months until the reduction in K_r was recognized and acted upon. For these reasons, the Work Group developed an alternative scheme that limited the downward adjustment in spKt/V for K_r to 2 mL/min, even for patients with higher levels of K_r. The decision to "cap" the reduction in session Kt/V was based on the lack of outcomes data in patients who have higher levels of RKF and receive very low amounts of dialysis Kt/V. Maintaining a minimum "total Kt/V" value of 1.2, using an exact calculation of the required dialysis spKt/V as described in the Appendix, would allow reduction of the dialysis dose down to near zero at levels of RKF that are below the threshold for initiating dialysis. The wisdom of recommending this fully incremental approach was intensely debated in the Work Group. Opinions differed, so it was decided to leave further reductions in dialysis dose, below values suggested in Table 13, to the discretion of the clinician. One single study[81], addressed this issue but there are few other studies of outcomes in patients with RKF hemodialyzed using an incremental dialysis schedule. This remains a critical area where more research is recommended.

Second, it was recommended that in patients for whom treatments are reduced because of K_r of 2.0 or greater, K_r should be rechecked at least quarterly (every 3 months) and after any event suspected to be associated with a sudden decrease in K_r. However, because the Work Group did not want to impose a burden of verifying K_r for all patients in a dialysis clinic, the recommendation is to verify it only in patients for whom the target dialysis dose is reduced.

Increase in Minimally Adequate Dose for Special Populations (CPR 4.5)

One potential area of concern relates to selected subgroups of patients who may require more dialysis. During the design phase of the HEMO Study, 7 such subgroups were postulated, including patients with high comorbidity scores, patients with diabetes, high-vintage patients, Caucasian patients, and women. Based on HEMO Study results plus

results from subsequent cross-sectional studies plus clinical judgment and "common sense," the Work Group recommended possibly increasing the target dose of dialysis in 2 groups of patients: women and small patients.

Women. Of the 7 "high-risk" groups identified during the design phase in the HEMO Study, an interaction with dose group assignment was present for only women (Table 8).[13] Women assigned to the higher dose of dialysis (URR ;75%, on average) had better survival than those assigned to URR of about 63%. The overall benefit for men and women was close to zero because an opposite nonsignificant trend for increased mortality in men assigned to the higher dose of dialysis also was found. As best could be determined, the sex-dose-mortality interaction was not caused by body size, although most women in the HEMO Study had a smaller body size, determined by using a variety of measures, with little overlap with the men in the study. While the HEMO Study was in progress, others identified a similar sex-dose interaction,[57] and after HEMO Study results were reported, another group reported a similar association in the USRDS-Medicare database.[104]

To complicate matters, the dose-targeting bias (discussed in more detail in Guideline 4) appeared to be enhanced in women compared with men.[98] This means that observational data should not necessarily be considered confirmatory of the intent-to-treat sex-dose-mortality interaction identified in the HEMO Study. However, because both randomized and observational data suggested that a higher dose of dialysis might be beneficial for women, the Work Group was comfortable with issuing a CPR for considering a higher dialysis target dose in women. For the most part, this happens naturally because most women have a smaller value for V; thus, the same prescription applied to a man and a woman, even considering patients of equal weight, will result in a higher Kt/V in the woman.

Body Size. There are, of course, multiple reasons why a patient can be "small." A patient can be short, small boned, or simply thin, all without being malnourished. Most data examining body size versus dose versus mortality interactions looked at anthropometric measures in which body size was derived from weight and height—eg, body mass index (BMI)—and, in some studies (in which Watson V was used), sex, and age. It appears that most of the mortality effect in these studies is related to BW because the Work Group was not able to find data in which patient height was a predictor of mortality (nor was height a predictor of mortality in the HEMO Study). It is then presumed that patients with lower BMI or Watson V primarily are underweight patients who are malnourished.

A separate issue is whether smaller nonundernourished patients who are at or near their expected weight might require more dialysis. Here, the argument has to do with sizing delivered dose of therapy based on body water, which is a factor of BW to the 1.0 power (usually V = some factor multiplied times the postdialysis weight). GFR usually is sized according to BSA, which is a factor multiplied times BW raised to the 0.667 (2/3) power. If Kt was normalized to BSA or some factor multiplied by $V^{0.667}$ and a single target value was assigned for all values of weight, the result would be that more dialysis would be assigned to smaller patients than with the current Kt/V strategy, and less dialysis

would be assigned to very large patients. The argument has been made that V is determined substantially by skeletal muscle mass, which may be relatively quiescent in terms of generation of uremic toxins. Although women or less muscular men may have a smaller V than similar-height controls, it does not necessarily mean they require less dialysis.

The Work Group noted and reviewed a number of studies in this field, examining the relationship of Kt and various measures of body size. Most of these analyzed the Fresenius North America patient data set.[78,101]

The Work Group also looked at an analysis of survival by various body size parameters in the HEMO Study,[13] in which various measures of body size were not found to interact with delivered dose. The Work Group concluded that there was not sufficient evidence to abandon the concept of sizing of dialysis dose according to V for the moment because cross-sectional survival analyses of dose versus mortality have so many biases that—at present—the effects of individual confounding factors have not been completely clarified. Furthermore, there is great simplicity in being able to monitor delivered dialysis dose based on URR and then combine this with weight loss and other information to compute a delivered Kt/V.

The compromise solution for the present update was to keep the dose as spKt/V and the minimum dose unchanged, as per the KDOQI 2000 guidelines, but to issue this CPR, which recommends that one consider increasing minimum dialysis dose targets in both women and small patients.

Several logical questions arise:

- By how much should the targets be increased?
- Should targets be increased for both large women and small women?
- In small women who also are "small" in terms of their size, should the increase in dose be greater than the increase for small men?

The Work Group decided to leave these decisions up to the practitioner, although an increased minimum dose of 25% was the range of increase in dose envisaged for either women or small patients (eg, to an spKt/V of 1.5 for a thrice-weekly schedule with $K_r < 2$).

Dialysis Adequacy for Patients Who Are Malnourished and/or Losing Weight (CPR 4.6)

Because nutrition tends to deteriorate even at relatively well-preserved levels of renal function,[288] the notion is prevalent in the dialysis community that increasing the amount of dialysis may help improve nutritional status. A variety of nutritional parameters were measured in the HEMO Study, and the higher-dose group did not show improvement in any of the nutritional parameters measured, including serum albumin, anthropometrics, or food intake. However, patients treated with longer (8-hour) periods of dialysis given 3 times per week or patients following 6-times-per-week short-daily dialysis regimens or nocturnal-dialysis regimens sometimes reported marked benefits in terms of food intake, serum albumin level (although this is confounded by blood volume changes caused by hemoconcentration), and increase in dry BW.[284]

For these reasons, the Work Group issued the present CPR, which recommends that practitioners consider increasing the dose of dialysis in a thrice-weekly framework in patients who are judged to be malnourished by BW criteria, subjective global assessment, or other means. The lack of a beneficial effect on nutritional parameters in the HEMO Study of increasing spKt/V from 1.3 to 1.7 suggests that perhaps a more useful strategy in such patients is to increase dialysis frequency, although it is recognized that such therapies are not uniformly available at all centers.

Dialysis Adequacy for Patients Who Are Hyperphosphatemic or With Refractory Volume Overload and Other Categories of Patients Who Might Benefit From More Frequent Dialysis (CPR 4.7)

Patients With Hyperphosphatemia. Serum phosphorus level appears to be a robust predictor of mortality in dialysis patients, as well as patients with CKD.[286] Phosphorus control is dependent on phosphorus intake, compliance with phosphorus-binder intake, and HD prescription. Because serum phosphorus level decreases to a low level early in dialysis, increases in Kt/V in a thrice-weekly framework while holding treatment time constant (eg, by increasing blood flow rate or dialyzer urea clearance) or slight increases in dialysis treatment time are expected to have only a mild to negligible effect on serum phosphorus levels. With short-daily dialysis schedules, the initial 30 minutes of each treatment occurs while serum phosphorus levels are still high, but overall serum phosphorus control has been disappointing, especially using short (1.5- to 2-hour) treatments. Patients undergoing short-daily dialysis sometimes increase their food or protein (and therefore phosphorus) intake, which may compensate or even override the small additional amount of phosphorus removal. A recent nonrandomized study in which 3-hour treatments were given 6 times per week showed a decrease in serum phosphorus levels.[200] However, it is not clear to what extent patients would tolerate 3-hour treatments given 6 days per week or if alternative measures to control serum phosphorus might be equally or more effective.

An increase in total weekly hours of dialysis, probably more than 24 h/wk, distributed over at least 3 treatments per week appears to be needed to control phosphorus levels in most dialysis patients. In the Tassin experience (8 h/wk $\times$ 3 = 24 h), approximately one third of patients no longer required phosphate binders (B. Charra, personal communication, February 2005). Using an "every-other-night" nocturnal dialysis strategy ($\sim$28 h/wk) should give results similar to those in the Tassin experience. Nocturnal dialysis given 5 to 6 times per week appears to remove the need for phosphorus binders, adequately controls phosphorus levels in almost all patients, and often requires the addition of phosphorus to the dialysate to prevent hypophosphatemia.[284]

Volume-Overloaded Patients. Control of patient volume and blood pressure are reviewed in detail in Guideline 5. In addition to the recommendations discussed in Guideline 5 regarding sodium balance, one of the most reliable methods to help achieve volume control is to extend total weekly dialysis time. In cases in which this cannot be done practically in a thrice-weekly framework, a 4-times-per-week schedule has proved

useful. Additional benefits may be obtained by moving to a short-daily or not-so-short daily 6-times-per-week schedule, and ultimate control would be expected using a nocturnal HD schedule.

Other Categories of Patients for Whom More Frequent Dialysis May Be Beneficial. At the present time, other patient subgroups that might benefit from more frequent dialysis are not as clearly identified. It remains possible that almost all patients might benefit, although practical and reimbursement issues, as well as the present incomplete state of knowledge, clearly preclude such a recommendation. Small largely uncontrolled studies suggest that—in addition to improved nutritional status, serum phosphorus, and volume control—more frequent dialysis may improve erythropoietin sensitivity, quality of sleep, and sleep apnea, as well as overall QOL.

The Minimum Dialysis Treatment Time for 3 Treatments per Week With K_r Less Than 2 mL/min Should be 3 Hours (CPR 4.8)

This guideline evolved from 2 considerations. The first is the concept of attempting to maintain stdKt/V close to 2.0 per week as a minimum amount of dialysis across all schedules. For a 2-hour dialysis treatment, an spKt/V of at least 1.4 is required to achieve an stdKt/V of 2.0. The second consideration is that it is difficult to achieve good control of salt and water balance with very short treatment times. The outcomes evidence for this CPR is not particularly strong; in the HEMO Study, the minimum treatment time was 2.5 hours and there was no randomized evaluation of treatment time; thus, the HEMO Study is not applicable here. A study that compared conventional dialysis (3- to 4-hour treatments) with ultrashort high-efficiency hemodiafiltration found no difference in level of blood pressure control.[289]

Very recent studies, including 1 RCT, suggested that dialysis treatment time has an impact on outcomes.[72A] Cross-sectional data showed that dialysis treatment time was related inversely to mortality, but much of this effect disappeared when patient BSA was included in the model.[101] It was the Work Group's belief that a minimum treatment time of 3 hours reflects clinical practice and was especially important in patients with a low K_r (<2 mL/min).

LIMITATIONS

Given the difficulty conducting RCTs in the HD population, many of the questions addressed by the present CPRs will not be answered definitively with Level A evidence for many years. It takes approximately 2,000 patients to run a randomized trial powered to detect a change in mortality (eg, the HEMO trial), and even then, the power to detect smaller effects is limited.

The level of β2M clearance in the HEMO Study was modest, and it is unclear whether more definitive benefits of convective and/or high-flux treatment might be seen with high-substitution volume hemodiafiltration, in which levels of β2M clearance substantially greater than those obtained in the HEMO Study can be achieved.

The Work Group believes that given the dose-targeting bias identified in the HEMO database[98] and the multiple confounding factors present in assignment of dialysis dose,

modeled volume, and different survival effects caused by body size, it is difficult to draw valid conclusions about how best to target dialysis therapy based on body size. The present guidelines address the issue of increasing the amount of minimal dialysis for smaller patients. They do not address the issue of reducing the amount of minimal dialysis for very large patients, for which technical and time issues become burdensome for both staff and patient.

With regard to more frequent therapies, the Work Group understands that their use is growing markedly. The present time should be one of experimentation in terms of finding the best combination of schedules and treatment times, and the Work Group was accordingly restrained in terms of its recommendations for how best to deliver such therapies.

CLINICAL PRACTICE RECOMMENDATION 5: DIALYZER MEMBRANES AND REUSE

Selection of dialyzer membranes and reuse practices are not included in the prescription of small-solute clearance, yet they can be important determinants of patient survival and QOL.

5.1 When dialyzers are reused, they should be reprocessed following the Association for the Advancement of Medical Instrumentation (AAMI) *Standards and Recommended Practices* for reuse of hemodialyzers.[291]

5.2 Dialyzers intended for reuse should have a blood compartment volume not less than 80% of the original measured volume or a urea (or ionic) clearance not less than 90% of the original measured clearance.

5.3 The use of poorly biocompatible, unmodified cellulose dialyzer membranes for HD is discouraged.

RATIONALE

Hemodialyzer Reprocessing and Reuse (CPR 5.1)

Thorough examination of data pertaining to the impact of reused dialyzers on patient safety was beyond the scope of the HD Adequacy Work Group. Therefore, the Work Group takes no position for or against the practice of dialyzer reuse.

Reprocessing dialyzers for reuse in the same patient was popularized 2 to 3 decades ago to allow widespread use of the more biocompatible and higher flux dialyzers that are more expensive than their less biocompatible and lower flux counterparts. Reuse of the former more expensive dialyzers remains a common practice in the United States today.[41,292–297] In 2002 in the United States, 78% of HD clinics reprocessed dialyzers,[41] but—largely as a result of declining prices and the recent decision of a major dialysis provider (Fresenius Medical Care, US) to discontinue reuse—fewer US dialysis patients are enrolled in reuse programs today.

Reprocessing of disposable medical devices designed for single use as a cost-saving measure has been debated, not only for dialyzers, but also for sundry and other medical devices.[297] In the case of dialyzer reuse, the main concern has been the risk to life, but other issues have been raised, such as risk for infection and pyrogenic reactions, toxicity from disinfectants, reduced dialyzer performance,[297] impaired removal of large molecules,[294] and the validity of the dialyzer blood volume measurement as a criterion for assessing dialyzer function.[292,298]

Over the years, a plethora of publications have addressed the possible cause-and-effect relationship between reuse and mortality. Conclusions reported in earlier publications were conflicting, possibly because reuse-related morbidity and mortality is a moving target (Table 14). Practice patterns, reuse procedures, dialyzer membranes, comorbidity, age difference, nature of the primary disease, disease severity, ethnic make-up, and other potentially confounding influences have evolved over time. For example, high-flux synthetic membranes have almost completely replaced low-flux cellulosic membranes. Whereas the number of times that a dialyzer is reused varies from clinic to clinic, the average number of reuses per dialyzer is higher (>15) in recent years compared with earlier years (<10).[294]

Table 14: Effect of Dialyzer Reuse on Mortality

Author, Year	Study design	N	Follow-up (maximum)	Applicability	Predictor	Results			Quality
						Effect Size	95% CI	P Value	
Lowrie, 2004[256]	Retrospective cohort	61,122	(1 yr)	↑↑	Single use vs. Reuse	HR=0.90	0.84, 0.97	0.005[a]	○
Collins, 1998[125]	Retrospective cohort	13,926[b]	(2 yr)	↑↑	Peracetic acid reuse vs. Single use	RR=1.15	1.01, 1.31	<0.05	○
		20,422[c]	(3 yr)			RR=1.03	0.92, 1.15	NS	

a. Multivariate analysis after a lag of 120 days from discontinuation of reuse in the single use group
b Prevalent cohort 1988-1990
c Prevalent cohort 1991-1993

The sterilant used also has varied from clinic to clinic and over time. During 1983 to 2002, the percentage of centers using formaldehyde for reprocessing dialyzers decreased from 94% to 20%, whereas the percentage using a peracetic acid preparation increased from 5% to 72%. In 2002, a total of 4% of centers used heat or glutaraldehyde to disinfect dialyzers between reuses.[295] Also, the number of times that a dialyzer is reused varies from clinic to clinic. Because of these various confounding factors, research data obtained from decades-old studies may have less present-day clinical relevance.

In one of the largest retrospective analyses, 1- to 2-year follow-up data were examined in a representative sample of 12,791 patients treated in 1,394 dialysis facilities from 1994 through 1995.[297] After adjustment for other risks, RR for mortality did not differ for patients treated in clinics that reused dialyzers compared with patients from single-use clinics. In addition, among patients at clinics that reused dialyzers, high-flux synthetic membranes were associated with lower mortality risk, particularly when exposed to bleach.[297] However, a recent study found a patient survival advantage when the patient was switched from reuse to single use.[299] It was suggested that because the cost of biocompatible membranes has decreased of late, it might be time for dialysis clinics to consider abolition of the reuse practice.[300] However, the cost of single-use biocompatible dialyzers is still considerable, and most investigators continue to maintain that the practice of reuse is safe,[301,302] provided it is performed according to recognized reuse protocols, including the dialyzer manufacturer's instructions.[292,295,296,303]

In an analysis of 49,273 incident Medicare patients from 1998 to 1999, no significant differences in mortality or first hospitalization risk were found among patients treated with single-use dialyzers compared with dialyzers cleansed by using different reprocessing techniques.[238] In a recent review of published reports, adjusted Medicare and Centers for Disease Control data from the early to mid-1990s showed no measurable mortality risk from reuse.[239] In accordance, recent Medicare data also showed no survival advantage associated with single use in incident US patients during 2001.[304] In addition, no differences in mortality were found among for-profit, not-for-profit, hospital-based, and free-standing clinics. To date, no prospective RCTs of dialyzer reuse have been carried out.

The delivered dose of dialysis may decrease as a result of dialyzer reuse.[306–310] The previous Work Group was particularly concerned by the apparent dialysis center– specific effect of reuse on delivered Kt/V, suggesting that the process of dialyzer reuse and/or its monitoring may be problematic. Recently, more encouraging results generated by the HEMO Study showed that average loss of urea clearance was only 1% to 2% per 10 reuses for both low-flux and high-flux membranes reprocessed with different germicidal regimens.[310] Focusing on larger molecule removal, the same study showed that reuse of high-flux dialyzers made of different membrane materials and reprocessed with different germicides brought about widely disparate clearances of β2M.[310] For example, β2M clearances increased markedly by using high-flux polysulfone dialyzers reprocessed with bleach, whereas reprocessing the same dialyzer with peracetic acid appeared to have the opposite effect.[310]

The Work Group recommends that dialysis facilities choosing to reuse dialyzers follow the AAMI recommendations for reprocessing while remaining alert to the possibility that reuse may adversely affect adequacy of the delivered dialysis dose. AAMI recommenda-

tions were prepared by a panel of experts and offer practical reuse procedures that have been adopted by the CMS, formerly Health Care Financing Administration. These recommendations represent the best guidance available on dialyzer reuse procedures.

Monitoring Reuse (CPRs 5.1 and 5.2)

Because small-solute clearance is the major function of the dialyzer and clot formation within the blood compartment reduces clearance, sometimes irreversibly, a method for monitoring clearance with each reuse is required to avoid underdialyzing the patient. Dialyzer blood compartment volume, sometimes called "total cell volume" (TCV) or "fiber bundle volume," is an indirect measure of the total membrane surface area available for diffusive transport. It is measured easily by displacement of air or water during the reprocessing procedure.[291] As surface area is lost because of clotting, solute clearances decrease, putting the patient at risk for underdialysis. This risk would go undetected in a clinic that does not measure clearances or TCV with each reuse.[306,308–311] Changes in TCV were shown to correlate well with changes in small-solute transport characteristics of hollow-fiber dialyzers, although the relationship is not linear.[307,312,313] A 20% loss of TCV correlates with only a 10% loss of clearance because the (now) higher velocity in the remaining functioning fibers leads to an increase in average diffusion rate within each fiber.[291,313,314] To allow accurate measurement of these changes, TCV should be measured before the first use and during each subsequent reuse processing. The first measurement is required because of possible variability among dialyzers and dialyzer lots. The Work Group did not consider using the average volume among dialyzers of a given model or lot as an acceptable substitute for this measurement before first use.

In vitro determination of TCV may not detect loss of surface area caused by clotting during dialysis.[315] However, during routine dialysis in a representative group of patients who underwent adequate anticoagulation during each dialysis treatment, no differences were found between TCV values measured by using an ultrasound detection method applied during dialysis and conventional volume displacement measurement after dialysis.[316]

In the place of TCV as an indirect yardstick of dialyzer function, direct measurements of ionic clearance (also known as conductivity or sodium clearance) or urea clearances also can be used to evaluate dialyzer function because results of these clearance values correlate closely with one another and TCV results.[74,291,317–323] A variety of dialysate delivery systems have the capacity to perform noninvasive, automated, on-line determination of a dialyzer's ionic clearance.[318,319,323] The Work Group agrees with the AAMI that TCV, ionic clearance, and urea clearance can all be used to assess the function of either fresh or reused dialyzers.[76,317]

Because a 10% decrease in urea clearance could lead to inadequate dialysis if the dialysis prescription was marginal to begin with, the Work Group agrees with the position of the AAMI that a change in urea clearance of $\pm$10% is acceptable as long as the patient's dialysis prescription takes into account the 10% loss in such clearance (20% loss in TCV) that may occur with dialyzer reuse.[291] This criterion of $\pm$10% clearance change also should apply to ionic clearances when they are used as yardsticks because ionic clearance

was shown to correlate closely with urea clearance.[291] Finally, monitoring relevant patient data is recommended to ensure that all parameters relating to dialyzer clearance are being met. Specifically, examination of Kt/V and/or URR over time is needed. The failure of these results to meet the expectations of the dialysis prescription should be investigated.[291]

When TCV measurements are used to evaluate dialyzer function before the first use, the rinsing associated with the reprocessing procedure may help remove undesirable dialyzer residuals (such as ethylene oxide,[324] bore fluids, potting compound [eg, polyurethane] fragments, dialyzer membrane fragments, plastic components, and other noxious substances remaining after dialyzer manufacture). In this regard, it is now a not-uncommon practice for centers (regardless of whether practicing dialyzer reuse) to "preprocess" dialyzers before their first use to minimize the introduction of harmful manufacturing residuals into the bloodstream.[300]

Dialyzer Membranes (CPR 5.3)

Dialyzer membranes can be classified into low-flux or high-flux varieties in accordance with their ultrafiltration coefficient (Kuf) and large-molecule clearance. The HEMO Study suggested that membranes with β2M clearance less than 10 mL/min be regarded as low flux, whereas those with β2M clearance greater than 20 mL/min and Kuf of 14 mL/h/mm Hg or greater may be classified as high flux.[270] Another classification recommended that dialyzers with Kuf between 4 and 8 mL/h/mm Hg be regarded as low flux, whereas those with Kuf greater than 20 mL/h/mm Hg be regarded as as high flux.[325] Both cellulose and synthetic membranes can be either low flux or high flux.

A thorough examination of all available data concerning the pros and cons of the use of the myriad varieties of dialyzer membranes was beyond the scope of the Work Group. The reader is referred to standard texts and relevant publications for more information.

In the past, most cellulose membranes were primarily hydrophilic and synthetic membranes were primarily hydrophobic. However, more recent synthetic membranes can possess mixed hydrophobic-hydrophilic structures.[325] Unmodified cellulose dialyzers had enormous popularity in the past, mainly because of their availability and low cost, but their use has been associated with a variety of abnormal biochemical changes in the blood.[326] One of the main causes for these unfavorable changes centers on activation of the alternate complement pathway with the resultant formation of detrimental anaphylatoxins.[327] Other adverse effects involve impairment of granulocyte function, including phagocytosis, adhesion, and formation of reactive oxygen species,[328] and, in the presence of other factors, facilitation of cytokine production by peripheral-blood mononuclear cells. An example of the latter phenomenon is depicted as follows: unmodified cellulose membranes and certain modified cellulose membranes allow, by diffusion, more ready passage of pyrogens (eg, endotoxins and their fragments) into the blood from contaminated dialysate than such synthetic high-flux membranes as those of polyamide, polyacrylonitrile, and polysulfone—despite the larger pore size of the high-flux membranes.[329,330] Pyrogens can promote the formation of deleterious cytokines by circulating peripheral-blood mononuclear cells that previously were stimulated by exposure to unmodified cellulose membranes.[331,332]

With regard to the possible impact of the use of unmodified cellulose membranes on patient morbidity and mortality, suffice it to say that investigations carried out to date provided conflicting results.[333] A number of studies suggested that low-flux unmodified cellulose membranes are inferior to high-flux synthetic ones in terms of patient mortality.[297,328,334,335] Conversely, no differences in mortality were found in certain comparative studies.[280,336] Furthermore, the Cochrane Database of Systematic Reviews did not find evidence of benefit when synthetic membranes were compared with cellulose or modified cellulose membranes with regard to mortality and dialysis-related adverse effects.[273] Finally, in patients dialyzed with unmodified cellulose membranes, no acute clinically detectable ill effects that could be related to complement activation were observed.[337,338] Investigations that control for the confounding influences of age, sex, race, duration of renal failure, duration and type of prior dialysis treatments, primary disease, RKF, nutrition status, degree of fluid overload, calcium $\times$ phosphorus product, hyperparathyroidism, hyperlipidemia, acidosis, anemia, comorbidities (such as diabetes, hypertension, heart failure, and other cardiovascular ailments), dialyzer single use or reuse (if reuse, method of sterilization), membrane flux, dialysis adequacy, and so on are difficult to perform. Such confounders might help explain the conflicting results encountered to date. In summary, to date, no unequivocal evidence has come forward supporting the notion that biocompatible synthetic membranes are definitely superior to their less biocompatible cellulose-derived counterparts.

Not all cellulose membranes behave in the same manner when interacting with the body. For example, unmodified cellulose membranes activate complement to a greater extent than modified cellulose membranes, such as those of various cellulose acetates, whereas some of the modified cellulose membranes tend to activate complement to a greater extent than synthetic membranes.[339,340] Because of differences in the biological behavior of the various categories of cellulose membranes, data derived from the use of functionally diverse dialyzers should be evaluated separately.

Many synthetic membranes have the capacity to adsorb endotoxins and β2M to various extents. Adsorption of endotoxins is related to the provision of binding sites for bacterial products by the hydrophobic domains of the synthetic membranes.[329] Adsorption of β2M by membranes made of polysulfone, polyacrylonitrile, polyamide, polymethylmethacrylate, and polycarbonate[279] is believed to be a function of the electrical charges distributed both at the surface and in the substance of the membrane.[341,342] It should be noted that high-flux membranes (whether cellulose or synthetic), because of their greater porosity, remove such large molecules as β2M (molecular weight, 11,815 d) to a greater extent than low-flux cellulose or low-flux synthetic membranes, often decreasing serum levels.[277,280,343–346] Accumulation of β2M in high concentrations promotes its polymerization to cause β2M amyloidosis.

Use of high-flux synthetic polyacrylonitrile membranes has brought about a lesser incidence of the amyloid-associated carpal tunnel syndrome and cystic bone lesions than the use of low-flux cellulose membranes.[282] Furthermore, high-flux dialysis using polysulfone membranes was reported to postpone clinical manifestations of dialysis-related amyloidosis.[347] In 1 study, prolonged use of high-flux synthetic membranes led to improvement

in carpal tunnel syndrome and patient mortality.[348] In the HEMO Study, although high-flux membranes did not cause a statistically significant improvement in mortality, predialysis serum β2M levels were found to be a good predictor of mortality.[349]

Because unmodified cellulose membranes have no known advantages over synthetic membranes other than lower cost, and unmodified cellulose membranes can markedly activate complement and bring about other potentially adverse effects in the blood, it would seem prudent to dialyze patients with the more biocompatible and less complement-activating membranes.[279] This suggestion is strengthened because long-term effects of intense complement activation and other untoward interactions with blood are largely unknown. However, it equally could be argued that because of their lower costs, unmodified cellulose dialyzers would allow the implementation of otherwise cost-prohibitive, but life-saving, dialysis therapy in some developing countries.[350] Because synthetic membranes are more biocompatible, cause less complement activation, and can adsorb endotoxins and β2M, their use is favored.

CLINICAL PRACTICE RECOMMENDATIONS FOR GUIDELINE 6: PRESERVATION OF RESIDUAL KIDNEY FUNCTION

Several actions and precautions are recommended to preserve and enhance RKF.

6.1 Angiotensin-converting enzyme (ACE) inhibitors and/or angiotensin receptor blockers (ARBs) are agents of choice in HD patients with significant RKF and who need antihypertensive medication. Other measures to protect native kidneys are listed in Table 15.

6.2 Insults known to be nephrotoxic (eg, see Table 16) in patients with normal or impaired kidney function should be assumed, in the absence of direct evidence, to be nephrotoxic for the remnant kidney in HD patients and therefore should be avoided.

6.3 Prerenal and postrenal causes of decrease in RKF should be considered in the appropriate clinical setting.

BACKGROUND

Although the contribution of RKF to survival is well documented for patients managed with PD, the impact is less clear for those requiring HD. Most studies assumed that RKF is negligible and report survival as a function of delivered Kt/V_{urea}, ignoring the potential benefits associated with RKF. However, recent data support the notion that RKF is an important predictor of survival and delivered Kt/V_{urea} can be adjusted to reflect the presence of renal function.[81,230]

RATIONALE

RKF is an important contributor to dialysis adequacy, and adequacy was shown to impact on morbidity and mortality in patients with CKD stage 5.[53] In contrast to HD, RKF provides continuous clearance of both small and large solutes and helps attenuate the large fluctuations in fluid balance and blood pressure that are more pronounced in anuric patients. Urine volume permits more fluid and potassium intake, relaxing overall dietary restrictions and reducing the fluctuations in body fluid volumes between dialysis treat-

Table 15. Efforts To Protect RKF

Avoidance of nephrotoxic agents, especially aminoglycosides, nonsteroidal anti-inflammatory drugs, COX-2 inhibitors and radiocontrast media
Avoidance of excessive ultrafiltration and hypotension during treatment
Routine use of biocompatible dialyzer membranes
Routine use of bicarbonate-based dialysate
Aggressive treatment of severe hypertension
Use of ACE inhibitors and/or ARBs
Use of ultrapure dialysate

COX-2: Cyclooxygenase-2

Table 16. Potential Insults to RKF

Radiographic contrast dye administered intravenously or intra-arterially
Aminoglycoside antibiotics
Nonsteroidal anti-inflammatory drugs, including COX-2 inhibitors
ECF volume depletion
Urinary tract obstruction
Hypercalcemia
Severe hypertension
Withdrawal of immunosuppressive therapy from a transplanted kidney

ments that contribute to volume overload syndromes, hypertension, and cardiac hypertrophy.[351] Preservation of residual renal mass also has the potential to provide beneficial endocrine and potentially other functions that are not yet discovered.

To measure RKF, K_r can be calculated from a 24-hour urine collection for urea clearance. As for PD, 24-hour urine collections should be obtained at least every 4 months or when a decrease in RKF is suspected (eg, decreasing urine output or recent exposure to a nephrotoxin). Precautions and actions that have been recommended to preserve RKF are listed in Table 15.

The nephrotoxic insults listed in Table 16 are well known to cause injury to normal kidneys and kidneys damaged by a variety of diseases. It is reasonable to presume that these insults also are harmful to the remnant kidney and should be avoided if RKF is to be preserved for as long as possible. Please refer to the Guideline for Preservation of RKF in PD patients in the NKF KDOQI PD Adequacy Guidelines for further discussion of this topic.

Episodes of intravascular volume depletion that frequently occur during HD probably contribute to more rapid loss of RKF; therefore, efforts to maintain hemodynamic stability should be routine. Strategies to minimize hypotension during HD include avoidance of excessive ultrafiltration, maintaining the target hematocrit, reduction in dialysate temperature, increasing dialysate sodium concentration, and predialysis administration of an α agonist, such as midodrine. Avoidance of hypotension also helps ensure delivery of adequate dialysis and minimize symptoms during HD. Paradoxically, loop diuretics, which are implicated as a cause of worsening renal function when used overzealously in patients with CKD, probably benefit HD patients because they reduce the requirement for fluid removal during dialysis.

The more prolonged preservation of RKF in HD patients observed in more recent years has been attributed to numerous factors, including more widespread use of biocompatible membranes, high-flux dialysis, and use of bicarbonate instead of acetate buffers. There is general disagreement about which of these factors, if any, plays a role (Table 17). A recent prospective randomized study suggested that ultrapure water, when combined with high-flux dialysis, may benefit native kidney function.[232,352] Another

Table 17: Effect of Pharmacologic Interventions on Loss of Residual Kidney Function

Author, Year	Study design	N	Follow-up (maximum)	Applicability	Predictor	Outcome Definition	Results			Quality
							Effect Size	95% CI	P Value	
Schiffl, 2002[233]	RCT (analyzed as a single cohort)	30	(24 mo)	↑	Dialysis Fluid (CFU/mL)	RRF loss	β= -0.450	-2.415, -0.251	0.02	O
					ACE inhibitors vs. None		β= -0.168	-0.152, -0.072	NS	
Moist, 2000[233]	Retrospective cohort	811	(18 mo)	↑↑	ACE inhibitors vs. None	RRF loss: Urine output <200 mL/24 h at the time of follow-up	OR=0.71		NS	O
					HMG CoA reductase inhibitor vs. None		OR=0.56		0.03	
					Biocompatible membrane vs. Cellulose		OR=0.84		NS	

study of high-flux biocompatible membranes with bicarbonate buffer and ultrapure water showed a decrease in RKF similar to that in a contemporary group of CAPD patients.[229] The more prolonged exposure to membranes during nocturnal and daily-dialysis regimens hopefully will shed more light on membrane contributions.

Despite some early concerns about irreversible drug-induced renal disease,[353] it is now generally accepted that the decrease in renal function observed in most patients treated with ACE inhibitors and ARBs is reversible and renoprotective, even in patients with CKD stage 5.[230] However, the drug-induced decrease in GFR causes an increase in levels of BUN, creatinine, and other solutes and may decrease urine output; thus, consequences in HD patients are not all benign. Irreversible loss of renal function may occur in patients with ischemic renal disease treated with ACE inhibitors.

Severe hypertension is well known to damage normal kidneys acutely (malignant hypertension) and can cause ongoing damage over a period of years (hypertensive nephrosclerosis). In addition, most kidney diseases, especially those like diabetes that target the kidney vasculature or glomeruli, are exacerbated by hypertension. In some patients initiating HD therapy, the kidneys may have been damaged more acutely by severe hypertension. Control of hypertension after initiating dialysis therapy has been associated with improvement in RKF, sometimes allowing discontinuation of dialysis therapy.[354] These patients should be identified from the beginning, and special attention should be given to controlling blood pressure for the purpose of preserving and possibly improving RKF.

The Work Group encourages PD as a first choice of modality for patients initiating KRT for reasons outlined in the NKF KDOQI PD Adequacy Guidelines, but also as a means of preserving RKF. However, most patients are not candidates for self-dialysis outside of a clinic; thus, HD remains the most common initial modality choice for new patients. The same attention that is given to RKF in PD patients should be directed to this much larger group of HD patients.

LIMITATIONS

Use of the nephrotoxic agents listed in Table 16 is not always contraindicated because they may be required in special circumstances to relieve pain (eg, nonsteroidal anti-inflammatory drugs), treat a difficult problem (eg, ultrafiltration during dialysis), or complete a vital diagnostic test (eg, coronary angiogram).

III. Research Recommendations

RANKING OF RECOMMENDATIONS

Research recommendations have been grouped into 3 categories: critical research, important research, and research of interest. These rankings were made by the Work Group based on current evidence and the need for research to provide additional evidence for the current CPGs and CPRs. No attempt was made to rank research recommendations within each of the 3 research categories.

CRITICAL RESEARCH RECOMMENDATIONS

Guideline 1: Initiation of HD

It has been well shown that education and planning for kidney failure can improve patient outcomes, but optimal approaches have not been established. Answers to certain questions could help improve clinical outcomes while reducing costs. These questions include the approaches to education and planning for kidney failure in different demographic and cultural groups and their relative costs. How effective are video and internet-based educational materials? Are computer-interactive programs helpful? How can nephrologists, nurses, social workers, dietitians, pharmacists, other professionals, and patient volunteers work together most effectively to educate new kidney patients and families? What is the best training for kidney patient educators? How much of the educational role should nephrologists delegate? For example, can earlier teaching about dietary potassium allow more extensive treatment with ACE inhibitors and ARBs in patients with CKD? Can new approaches to early dietary education yield improved volume and phosphorus control when patients reach kidney failure? What are the psychological and behavioral consequences of early education about the prospect of eventual organ failure and the shortened life expectancy associated with kidney failure?

Estimation equations for GFR (Table 1, Guideline 1) should be examined in patients who produce unusually little creatinine, in particular, the elderly and patients with other chronic illnesses. A second important clinical group for which current estimating equations have not been validated is those with significantly decreased kidney perfusion, as occurs in patients with advanced heart failure.

Studies of the time to initiate replacement therapy are needed to determine the consequences of timing on survival, morbidity, and cost. Results of the IDEAL Study will be critical, but it seems unlikely to be definitive for all clinical subgroups. In view of racial differences in dialysis mortality rates, it seems plausible that response to early treatment might vary by race. The HEMO Study finding of differential dose effects in women also suggests the possibility that the response to early initiation also might vary by sex. Because of longer exposure to uremia, do patients with a slower decrease in GFR benefit from earlier initiation of kidney replacement therapy? Do patients with primary tubular disorders benefit from initiation of KRT at a higher level of GFR than patients with primary glomerular disorders? These questions should be addressed in particular groups of interest, including children and the elderly.

Guideline 2: Methods for Measuring and Expressing HD Dose

The ongoing Frequent HD Network will provide data that should be used to evaluate potential benefits of short-daily or nocturnal dialysis. If published uncontrolled studies showing better QOL are confirmed, efforts must be directed to provide more frequent dialysis in a less encumbering manner.

The conductivity method promises to eliminate the need for drawing blood before and after dialysis and can be applied to each dialysis treatment. Objective studies are needed to correlate the delivered dose measured by using conductivity (ionic) dialysate methods with both eKt/V and spKt/V determined by using classic blood-based methods. Testing is needed to show whether this method is a reliable substitute for the present technique.

Guideline 3: Methods for Postdialysis Blood Sampling

Because the amount of blood drawn from dialysis patients should always be minimized, it is desirable to minimize the volume of the discard sample when drawing blood from a venous catheter. Studies of how the ratio of discarded volume to catheter lumen volume affects BUN concentration would be of practical interest.

Because timing may be different in smaller patients with shorter circuit pathways, validation of the stop-blood-flow method and stop-dialysate-flow method for determining dialysis dose in children requires future research.

Guideline 4: Minimally Adequate HD

There are no reliable data regarding mortality that are not extremely susceptible to patient selection, and no RCT comparing mortality rates is foreseen in the near future. Whether more frequent dialysis reduces hospitalization rates may be answered by an RCT currently in progress (NIH Frequent HD Network trial), although this trial is underpowered to detect other than a very large reduction. However, it is powered to detect improvements in both QOL measures and left ventricular mass index; the latter is strongly related to "hard" cardiovascular outcomes.

An alternative measure of dialysis dose in units measuring conductivity is $K_{ecn} \times T/V_{ant}$, where K_{ecn} is the conductivity-derived dialyzer clearance, T = session length, and V_{ant} = anthropometric volume. Studies are needed to determine whether adequacy determined serially using a conductivity standard is more or less variable, and more or less reliable, than adequacy determined based on classical urea kinetics with predialysis vs. postdialysis BUN measurements. Studies are also needed to determine whether much of the same information gleaned from monthly pre- and postdialysis BUN measurements in terms of PCR could be obtained using monthly predialysis BUN measurements only, and quarterly pre/post BUN values.

Further study would look at the ratio of modeled to anthropometric volume, both cross-sectionally, and serially in large numbers of patients, and the possibility of dosing dialysis based on $K_{ecn} \times T/BSA$, where BSA is body surface area multiplied by a correction factor such that it would vary to the 2/3 power and in effect, reflect dosing based on body surface area.

Guideline 5: Volume and Blood Pressure Control

The cost of dialyzer and blood tubing disposal has a direct impact on reuse, which reduces this provider burden. Aside from the biological hazard, recycling of dialyzer and tubing materials could reduce the requirement for disposal site space. Studies of the potential economic benefits are needed.

Reuse of dialyzers and blood tubing may influence patient exposure to spallated particles, plasticizers, bore fluid, ethylene oxide, and other noxious manufacturing residuals from newly manufactured dialyzers. Studies should compare these exposures with the single-use situation when dialyzers and tubing are reused.

Guideline 6: Preservation of RKF

Additional comparative studies of outcome in patients with and without RKF are needed.[355] At the present time, many dialysis clinics do not measure RKF routinely and some do not measure it at all. Such studies would help resolve the critical question about the importance of RKF measurements. Perhaps even more helpful would be a controlled clinical trial in which the prescribed dialysis dose is adjusted or not in patients with significant RKF.

Some studies have implicated contamination of the water used to prepare dialysate as a cause of dialysis morbidity and mortality. Other studies suggested that ultrapure dialysate helps preserve RKF.[232] Additional confirmatory studies are needed to determine whether introduction of ultrapure dialysate into routine clinical practice would help preserve RKF and improve such clinical outcomes as blood pressure control, nutritional status, and QOL.

A trial of ACE inhibitors or ARBs should be done to evaluate the effectiveness of such agents in preserving RKF.

After dialysis therapy has started, diuretics often are prescribed for patients with good urine output to help with potassium balance and avoid excessive fluctuations in ECF volume and blood pressure. This practice may or may not help preserve RKF. Studies should address the effectiveness of various diuretic doses and whether diuretics should be advocated in patients with significant urine output to help preserve RKF.

For patients in whom the targeted prescribed dialysis dose is based on RKF, there is an obvious need to measure RKF, but the optimum frequency of measurements has not been determined. The optimum frequency may depend on the type of kidney disease and the patient's history of its progression.

Guideline 7: Clinical Outcome Goals

Additional studies are needed to validate the tools currently used to measure QOL and patient satisfaction within the diverse CKD stage 5 population. Interventions used to improve QOL and patient satisfaction should be evaluated to determine success in improving QOL, patient satisfaction, and clinical outcome. As standards of care are modified and new care strategies are introduced, there is need for periodic reassessment of the presently recommended dose of dialysis and its effect on patient mortality, hospitalization rates, QOL, patient satisfaction, and transplantation rates.

Guideline 8: Pediatric HD Prescription and Adequacy

The high rates of young adult HD patient cardiovascular mortality and morbidity,[356,357] psychological illness, and unemployment[358] compel pediatric HD patient study in the areas of inflammation, cardiovascular fitness, nutrition assessment and malnutrition treatment, and health-related QOL. Because many young adult patients are treated in pediatric programs and have the potential to develop morbidities in their pediatric years, there is a need to study these areas in pediatric patients. Measurement of HD small-solute clearance, preferably using either measured or validated estimated eKt/V, and nutrition, using nPCR, are critical to control for the dose of delivered dialysis and nutrition status in any pediatric HD outcome study. Recent recommendations from the European Pediatric Dialysis Working Group[359] provide an excellent basis in terms of the current state of the art in pediatric HD practice, from which future research should emanate to improve the care of pediatric HD patients.

IMPORTANT RESEARCH RECOMMENDATIONS

Guideline 1: Initiation of HD

Less critical questions include measurement of patients' preferences (in the technical sense of utility) for the states of education vs. ignorance regarding prognosis and choices. It also would be important to understand demographic and cultural determinants of preference variation. Finally, work is needed on the ethical implications of therapeutic attempts to influence patient preferences. These issues are all less critical as research priorities, not because they are less important, but because the findings are less likely to influence practice and policy in the short term.

Guideline 2: Methods for Measuring and Expressing the HD Dose

Tests of variance are needed for Kt/V measured in patients receiving daily dialysis treatments. Theoretically, the variance will be larger because measured BUN values will be considerably lower and excursions from predialysis BUN to postdialysis BUN also will be lower, which reduces the power of kinetic modeling. How much lower and how much variance have not been determined in an experimental setting. This study can be done simply by drawing predialysis and postdialysis blood samples several days in succession. If blood-based measurements of Kt/V are found to be less reliable in these patients, dialysate methods may be required to measure the delivered dose. However, dialysate methods are intrinsically less accurate for measuring Kt/V than blood-based methods,[364] so additional comparative studies will be required if the blood-based methods are found to be inadequate.

Guideline 3: Methods for Postdialysis Blood Sampling

A study of needlestick injuries in dialysis clinics might help promote the use of blood-sampling procedures that do not involve use of exposed needles. This is an area of obvious importance and interest for which very few data are available.

Guideline 5: Volume and Blood Pressure Control

More research should be devoted to reprocessing techniques for various types of dialyzer membranes made by different manufacturers, especially with regard to approaches involving heat and more biocompatible chemicals, such as citric acid.

Guideline 6: Preservation of RKF

Observational studies should include data to determine whether RKF serves to reduce fluctuations in serum potassium and bicarbonate concentrations and reduce ECF volume and blood pressure fluctuations.

Some patients with slowly progressive kidney disease might benefit from incremental dialysis frequency (initiation of HD at a frequency < 3 times per week). Studies are needed to determine whether such a practice would help preserve RKF in patients with significant urine output and those with a marginally functional renal allograft.

RKF imparts a stronger survival advantage than dose of dialysis. Investigations should explore potential kidney synthetic functions that, if preserved in the remnant kidney, may provide survival benefits not explained by level of GFR.

Guideline 7: Clinical Outcome Goals

There is a need for analysis of data linking clinical outcomes to recommended processes within the target goals. This would include analysis of the impact of specific KDOQI processes adjusting for established factors (eg, blood pressure control, hemoglobin A_{1c} [HbA_{1c}], lipid management, pharmacological therapy) that strongly influence clinical outcomes of HD patients. Periodically, there is a need for refining case-mix adjustments over time to reflect changes in relative contribution of traditional, nontraditional, and emerging risk factors as standards of care change.

Guideline 8: Pediatric HD Prescription and Adequacy

Recent data from a small pediatric study showed benefits of daily nocturnal HD in children. Additional study of daily HD treatment schedules and technologies should be undertaken in children.

RESEARCH RECOMMENDATIONS OF INTEREST

Less critical issues include the development of prediction instruments to allow estimation of time to symptomatic kidney failure on the basis of serial GFR estimates.

Less critical questions include measurement of patient preferences about the tradeoffs between the burdens and benefits of earlier therapy.

Investigation of dialysis creatinine kinetics would help assess the effect of muscle mass on outcome and compare somatic with visceral body mass as risk factors for survival.

Studies of large patient populations to correlate urine output with RKF would help determine whether urine volume-related cutoff values for ignoring RKF are useful.

Although the potential insults listed in CPR Table 16 are known to injure normal and partially damaged native kidneys, studies are required to indict each insult in patients with CKD stage 5. It is unlikely that controlled clinical trials will appear in the near future; therefore, observational studies are encouraged.

The benefits of RKF may relate more to renal mass than urine volume. This possibility should be considered in outcome studies. Also, it would be helpful to correlate kidney size with RKF to determine whether RKF is predictable based on size.

Appendix. Methods for Adding Residual Clearance to Hemodialyzer Clearance

Because the duration is short and the clearance is relatively low, RKF contributes little to the decrease in BUN levels during dialysis. The effect of residual urea clearance (K_r) is seen during the long interdialysis interval when it serves to decrease the predialysis BUN level, as shown in Fig 6. When K_r is zero, the interdialysis rise in the BUN level is linear in the absence of fluid gain. If K_r is greater than zero, the increase in BUN level between dialyses is curvilinear and concave downward, resulting in a lower predialysis BUN level, so less HD is required to maintain the same average BUN level.

In addition, the continuous nature of K_r provides a more efficient clearance, so simply adding the time-averaged K_r to time-averaged K_d underestimates the contribution of K_r to overall clearance. A quantitative relationship between K_r, K_d, and overall urea clearance can be developed by applying a mathematical model of urea kinetics. The goal is to determine how much of a decrease in K_d can be allowed to achieve the same level of BUN when K_r is added. The following simplified formula depicts the relationship between dialyzer clearance (K_d) in the absence of K_r, and lower dialyzer clearance (K_d') permitted in the presence of K_r.[360,361]

$$kK_r = K_dt - K_d't$$

K_r, K_d and K_d' are expressed in milliliters per minute; t is the duration of HD in minutes.

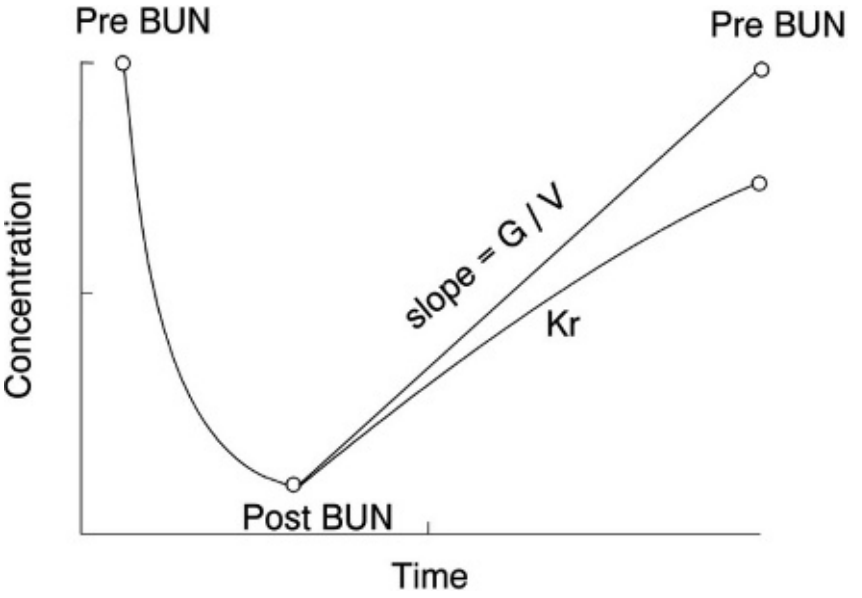
In this formula, k relates K_r to the difference between K_d and K_d', or the decrease in dialysis dose that is possible while still achieving the same BUN level that would be expected when there is no K_r. The parameter k has units of mL/(mL/min) and when multiplied by K_r permits an expression of K_r in equivalent dialysis units than can be spared. It can also be considered as a time or duration of K_r analogous to dialysis duration (t), but always is higher than the average interval between dialyses (t_i) because K_r is more efficient than K_d. When expressed per dialysis, the relationship among the reduced dialysis dose ($K_d't/V$), the required dose in the absence of K_r (K_dt/V), and the residual native kidney clearance (kK_r/V), is expressed by:

$$K_d't/V = K_dt/V - kK_r/V$$

where V is the patient's volume of urea distribution in milliliters.

In the absence of kinetic modeling, $K_d't/V$ can be solved by substituting the interdialysis interval (10,080 min per wk/frequency) for k in this expression. Note that this approach, shown in the first data column in Table 18, ignores the improved efficiency of the continuous RKF, but it is considered safe for the patient because it underestimates the effect of K_r.

Figure 6. Effect of residual native kidney clearance (K_r). The increase in BUN levels from the post-BUN level to the next pre-BUN level is modulated by K_r, as shown in the lower curve. The result is a pre-BUN level that is lower when compared to the pre-BUN level in the absence of K_r (upper line).



Another method to incorporate K_r into Kt/V is based on the equivalent clearance (EKR),[264] which represents the continuous equivalent of the patient's intermittent urea clearance and can be calculated as follows:

$$EKR = G/TAC$$

(G = urea generation rate; TAC = time-averaged BUN)

The result can be normalized to a typical V of 35 L and expressed in terms of nPCR and TAC using the equation for nPCR.[362]

$$nEKR = [35 \cdot (nPCR - 0.17)]/(5.42 \cdot TAC)$$

EKR is a total clearance that includes RKF, but the dialyzer component can be extracted by subtracting K_r. EKR is the continuous clearance necessary to maintain the equivalent TAC at the patient's nPCR. The EKR of intermittent HD can be directly compared to the EKR of patients dialyzed at any frequency or with the clearance of continuously functioning native kidneys. Routinely solving these equations requires the use of computational software.

Table 18. Values for *k* at Different Dialysis Frequencies and BUN Targets

Frequency	using T_I alone	Targeted BUN to hold constant	
		Time-Averaged*	Average Predialysis*
2	5040	6500	9500
3	3360	4000	5500
4	2520	2850	3700
5	2016	2200	2700
6	1680	1780	2100
7	1440	1500	1700

* The underlined numbers have been published.[261,262] The remainder were derived from urea kinetic modeling.

The use of EKR has been criticized because it fails to fully account for the improvement in efficiency associated with the continuous clearance of native kidneys or continuous dialysis. [267] Apparently, equating average urea concentrations ignores other more toxic solutes for which the difference in removal by continuous compared with intermittent clearance is greater than for urea. Equating "standard clearances" using the average peak BUN instead of TAC in the previous equation has been offered as a solution to this apparent problem.[265]

Instead of inflating K_r to match the relatively inefficient non-continuous dialyzer clearance as described above, an alternative method, favored by the Work Group, reduces the dialyzer clearance to a continuous equivalent clearance, based on normalizing the predialysis BUN. This continuous equivalent of a dialyzer clearance, also known as "standard

Table 19. Minimum spKt/V[a] Required To Achieve a stdKt/V[b] of 2.0 per Week

$K_r = 0$			
No. per Week	Td (hr)		
	2.0	3.5	8.0
2	--	--	3.00
3	--	1.22	1.06
4	0.87	0.77	0.68
5	0.64	0.57	0.51
6	0.51	0.45	0.40
7	0.42	0.38	0.34
$K_r = 2$ mL/min/1.73 m²			
No. per Week	Td (hr)		
	2.0	3.5	8.0
2	----	1.93	1.68
3	0.94	0.85	0.77
4	0.62	0.56	0.52
5	0.46	0.42	0.39
6	0.37	0.34	0.31
7	0.31	0.28	0.26

a. Dialyzer clearance only, expressed per dialysis

b. Calculated using a 2-compartment mathematical model. Assumptions: Patient with V = 35 L (should not matter); T_d is constant; K_e varies; ultrafiltration rate is 7 L/wk; nPCR is 1 g/kg/d (should not matter); dialyzed compartment is 1/3 of total V; K_r(urea) is 0 or 2 mL/min; symmetric schedule.

It is important to note that the minimum values for spKt/V shown in this table do not take into account reported improvements in outcome from increasing Kt/V when dialysis frequency is increase to more than 3x/week.

clearance"[265] (stdK) is the continuous clearance that maintains the BUN at a constant value equal to the average predialysis BUN achieved during intermittent dialysis. Because the pre-dialysis BUN is targeted, this approach gives results similar to that depicted in the third data column of Table 18. After normalizing the dialyzer clearance to stdK, K_r can simply be added to it because both can be considered continuous clearances. Dialyzer clearances (spKt/V) required to achieve a stdKt/V of 2.0 volumes per week are shown in Table 19 for treatment times that vary from 2 to 8 hours and for schedules from 2 to 7 treatments per week. These values were determined using a formal 2-compartment mathematical model of urea kinetics but similar results are obtained using the simplified equation for stdKt/V shown in section CPR2.

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III. Research Recommendations

PREAMBLE

RCTs are the optimal study design to answer intervention questions. A recent review concluded that between 1966 and 2002, the number of RCTs published in nephrology from 1966 to 2002 (2,779) is fewer than in all other specialties of internal medicine.[629] In addition, the overall quality of RCT reporting in nephrology is low and has not improved for 30 years. Issues identified included unclear allocation concealment (89%), lack of reported blinding of outcome assessors (92%), and failure to perform "intention-to-treat analysis" (50%). The challenges of improving the quality and quantity of trials in nephrology are substantial. We need to use standard guidelines and checklists for trial reporting, give greater attention to trial methods, and cease to focus on results of small underpowered studies. We must involve experts in trial design and reporting, expect multicenter collaboration, and do larger, but simpler, trials. Many of the research recommendations made in this section require multicenter trials to enroll sufficient patients to obtain clear-cut answers. Many will not receive external support from government or other grant agencies. However, they can be performed by collaboration between those in academic centers and those in clinical practice. We should emulate cardiology, for which there has been a 6-fold growth in clinical research trials, particularly in the number of patients (usually in the thousands) enrolled into the studies.

RANKING OF RECOMMENDATIONS

Research recommendations have been grouped into 3 categories: critical research, important research, and research of interest. These rankings were made by the Work Group based on current evidence and the need for research to provide additional evidence for the current CPGs and CPRs. No attempt was made to rank research recommendations within each of the 3 research categories.

Although the Vascular Access Work Group was restricted by the NKF to a thorough literature review in only 4 areas, the Work Group has developed research questions for all CPGs. These questions should not be viewed as comprehensive, but as a stimulus to the nephrology community to begin to ask, hopefully, better questions regarding vascular access with a goal of better outcomes for our patients.

CRITICAL RESEARCH RECOMMENDATIONS

Guideline 1. Patient Preparation for Permanent HD Access

Studies are required to determine the optimal vascular mapping criteria based on outcome goals of working fistulae.

Studies are needed to determine the optimal stratification of patients for fistula placement. Is there an age component to sizing of the artery and vein for fistula creation? Specifically, should the minimal vein diameter for such higher risk groups as female, diabetic, and elderly patients be larger to have acceptable working fistula outcomes?

Randomized studies should be performed comparing 1-stage with 2-stage brachial basilic vein transposition fistula outcomes.

Studies are needed to determine the optimal surgical techniques for fistula creation with outcomes to identify factors that minimize the development of surgical swing segment stenosis in fistulae.

Guideline 2. Selection and Placement of HD Access

Patients should be considered for construction of a primary fistula after failure of every HD access. There is a paucity of information about the success of this strategy. If a forearm loop AVG is placed as initial access, does this lead to successful construction of elbow-level fistulae? How often? Do we need an RCT? In what patients would a graft before fistula be cost- and resource effective? None? Some? Would a PU "immediate use" type of graft be preferable to a catheter if one had to do immediate (ie, within days) dialysis?

How often is primary conversion of dysfunctional grafts to fistulae successful? Is it affected by the previous history of thrombosis or angioplasty (if applicable)? What are the guidelines for number of angioplasties/thrombectomies performed before compromising the ability to convert to a fistula? What is the optimal timing for conversion?

The preference for fistulae is based on lower morbidity associated with their creation and maintenance compared with other access types. Is this still true for the US CKD stage 5 population? Has this remained true as the population has grown older and the health care system in the United States has been stretched? Late referrals, lower skill sets in the staff delivering dialysis and cannulating accesses, increased comorbidity in the United States compared with Europe, Japan, or Canada—do these factors influence the selection of initial access and the progression and choices among different access types?

Guideline 3. Cannulation of Fistulae and Grafts and Accession of HD Catheters and Port Catheter Systems

Can intensive structured cannulation training lead to better access outcomes?

Can increased remuneration for expert cannulators lead to better access outcomes?

Can self-cannulation lead to better outcomes?

Guideline 4. Detection of Access Dysfunction: Monitoring, Surveillance, and Diagnostic Testing

Studies are needed to compare outcomes of physical examination with "high-tech" methods in determining the best timing for intervention.

The role of DDU as an intermediate diagnostic test should be examined to determine the "timing" for access intervention with PTA or surgery.

There may be important differences in the susceptibility of grafts and fistulae to thrombosis as a function of absolute access flow or change in access flow over time. The "best" therapy for the access also may differ according to type. Future studies should carefully separate the surveillance data, type of intervention (PTA or surgical), response

to therapy, and both short-term and long-term outcomes according to access type, either graft or fistula. Because more proximal accesses have greater flow rates, data also should be categorized to access location, primarily the feeding artery (radial or ulnar versus low brachial, high brachial, and axillary for the upper arm and femoral for the thigh).

Studies are needed to establish objective criteria for endovascular intervention.

Guideline 5. Treatment of Fistula Complications

The efficacy of physical examination in detecting abnormalities in accesses difficult to cannulate should be studied.

Comparative trials are required to assess interventional versus surgical modalities to correct maturation failure with measurement of access flow longitudinally before and after correction.

Studies should examine the effect of intervention on: recurrent stenosis, elastic recoil, and juxta-anastomotic stenoses.

Guideline 6. Treatment of AVG Complications

Assessing adequacy of the intervention. Is PTA an effective intervention for treatment of vascular access–related stenosis? We cannot answer this question. A fundamental problem is our inability to reliably predict the outcomes of our percutaneous and surgical interventions. The true determinants of HD graft patency and longevity remain unknown. It certainly is a complex and multifactorial process. The primary determinants of graft failure likely are regulated by both physiological and genetic factors and therefore are variable within the patient population. To add to the confusion, neointimal hyperplastic stenoses develop simultaneously and sequentially in multiple locations. Our success in treating 1 stenosis is negated by the rapid development of another lesion. And there is another important variable: delayed elastic recoil can cause rapid recurrence of the stenosis after an apparently successful angioplasty procedure. This phenomenon can occur minutes to hours after balloon dilation, and our anecdotal experience suggests that elastic recoil of a stenosis may happen after 10% to 15% of our angioplasty procedures. Our current challenge is to identify the determinants for successful angioplasty and optimize our techniques to improve our clinical outcomes. In addition, we need to develop pharmacological means to reduce/prevent the recurrence of neointimal hyperplasia after successful angioplasty.

Criteria for success. An end point is used to define the successful completion of a procedure. The definition of a successful procedure can be viewed from several different perspectives. For example, the end point for clinical success is alleviation of the patient's symptoms. Hemodynamic success is restoration of normal blood flow throughout the treated vascular segment. And for treatment of stenoses, the end point for anatomic success is less than 30% residual diameter reduction. These clinical, hemodynamic, and anatomic end points serve as the determinants of a successful endovascular intervention. Our clinical experience has shown that these commonly used end points are *unreliable* for predicting the long-term patency of an HD graft or fistula. Although we use end points

to define immediate success, there is no postprocedural end point that correlates with long-term patency. Our inability to predict the long-term outcome of our endovascular procedures continues to frustrate both the physician and patient.

After an endovascular intervention, the standard definition of anatomic success is a residual stenosis with less than 30% diameter reduction. Although there are well-recognized physiological concepts that support the use of 50% stenosis as the definition of a hemodynamically significant lesion, there is no such scientific basis for the use of less than 30% residual stenosis to define a successful treatment. A consensus committee reached the value of 30% with representatives from interventional radiology and vascular surgery. This well-accepted standard end point (<30% residual stenosis) has no hemodynamic or physiological meaning. In addition, the residual stenosis does not allow for proper remodeling of the vein and may contribute to recurrence of stenosis. Therefore, it is not surprising that use of this parameter as a determinant of success is not predictive of the long-term patency of an HD graft or fistula. This poor correlation between degree of residual stenosis and subsequent patency was substantiated in a study that reported analysis of 96 interventions performed in native AVFs.[630] After angioplasty, 17 lesions had greater than 30% residual stenosis and, by definition, had failed treatment. However, there was no difference in the long-term patency of this group compared with patients who had lesions with less than 30% residual stenosis on final fistulography.

Obviously, criteria used for success need to be examined by well-designed outcome studies.

Multiple lesions and criteria for intervention. According to the KDOQI guidelines, lesions with less than 50% stenosis should not be treated. However, it is not uncommon for a graft or fistula to have multiple areas of endoluminal irregularity that, when measured individually, represent less than 50% stenosis and therefore should not be treated. However, a hemodynamic abnormality may still exist. The basic principles of hemodynamics state that the effects of multiple stenoses are additive, similar to an electrical circuit with a series of multiple resistors. Therefore, our current concepts that emphasize the evaluation of individual stenoses using anatomic criteria are flawed.

New methods[54] that provide a more global assessment of the entire vascular access circuit suggest that subtle lesions can have substantial hemodynamic effects. The assessment of intragraft blood flow during angioplasty procedures may provide additional information regarding the hemodynamic importance of lesions that are greater than 30% but less than 50% stenosis.

We need to identify physiological/objective criteria for successful intervention.

IMPORTANT RESEARCH RECOMMENDATIONS

Guideline 1. Patient Preparation for Permanent HD Access

Studies are needed to determine the optimum timing of access placement.

Studies should be performed to examine the effect of exercises to mature vessels (arterial and venous) before and after fistulae are constructed.

The use of diluted contrast to characterize the venous system peripherally and centrally in patients with CKD and the effect on residual kidney function should be studied.

Additional studies are needed to compare the accuracy of MRA and DDU in evaluating central veins.

How can we align incentives for the creation of fistulae for all stakeholders: patients, nephrologists, surgeons, and dialysis providers?

Guideline 2. Selection and Placement of HD Access

What is the relative benefit of arm exercises performed before or after fistula construction and maturation or both?

We need RCTs to determine the effect of exercise either before or after access construction, alone or combined, on access maturation, time to cannulation, primary and secondary patency, ease of cannulation, number of procedures needed during the life span of the access, and cost analysis. Is pressure inside the fistula important in the maturation process? Is it flow or intraconduit pressure or both that allow an access to tolerate cannulation without infiltration? Should a nonocclusive tourniquet be used during exercise? Do we use/measure mere clinical end points for these studies or does fistula flow need to be measured as well, or does it not matter what the flow is? Brachial artery flow can be measured as a surrogate for access flow.

If intrafistula flow is important, what flow is needed to mature a fistula?

Guideline 3. Cannulation of Fistulae and Grafts and Accession of HD Catheters and Port Catheter Systems

Additional studies are needed of disinfectants, the role of antibiotic locks, and which patients may benefit most from CVC salvage. Risk-benefit outcomes, as well as long-term antibiotic susceptibility studies, should be done to detect resistance.

Studies are needed to examine the effectiveness of data on rotation of sites, buttonhole, flow/pressure curves, and so on.

Does the bevel-up cannulation method decrease access complications?

What needle tip-to-tip measurements minimize recirculation or prevent erroneous access flow measurements?

Can buttonhole (constant-site) cannulation be used in biografts?

Should an infiltrating needle be removed after the patient undergoes sytemic anticoagulation with heparin?

How should the timing of flushing and locking of heparin in a catheter occur in a patient who is using 1 needle in the fistula and 1 side of the catheter for return?

Do transparent dressings, where the exit site is clearly visualized, need to be changed at each dialysis treatment?

Guideline 4. Detection of Access Dysfunction: Monitoring, Surveillance, and Diagnostic Testing

Further evaluation of the acoustic stethoscope is needed in detecting hemodynamically significant stenoses.

The relationship of access flow to pressure varies among individuals, affected chiefly by the health and capacity of the artery to deliver flow into the access. Within a population, there may be no obvious relationship between access flow and P_{IA} if measurements are made cross-sectionally because the important determinant in an individual is baseline flow (which may vary from 500 to 3,000 mL/min), the presence of 1 or more stenoses, their location, and the rate of evolution of the stenosis or stenoses. Additional studies are needed to determine the natural course of stenoses in grafts and fistulae. Stable stenoses may need no intervention if they are not associated with increased risk for thrombosis. Conversely, there may be significant risk for thrombosis, even with access flows exceeding 1,000 mL/min. Noninterventional trials should be conducted with the clock starting from the time of construction.

Large-scale trials are required to determine whether correction only of "hemodynamically" significant lesions (those associated with "low" access flows or "high" pressures or a change in access flow or pressure) is superior to correction of all stenosis greater than 50%.

Guideline 5. Treatment of Fistula Complications

Studies are required to compare strategies for treating aneurysms in fistula: surgery with new anastomosis versus surgical creation of new anastomosis. Cost and outcome analyses should be performed.

Studies are needed to examine the efficacy of endoluminal interventional versus surgical procedures for the management of aneurysms in fistulae.

Comparative trials should be performed to study the efficacy of surgery compared with interventional endoluminal procedures in correcting stenoses/thrombosis, with the same methods used for outcomes.

The role of thrombolytics in reestablishing or maintaining patency after fistula thrombosis should be examined. Low doses of thrombolytics have been used to keep costs controlled—does it make a difference in outcomes?

Data from RCTs are needed on the duration of thrombosis and success in reestablishing/maintaining patency. Is surgery more effective early or later?

Guideline 6. Treatment of AVG Complications

Assessing effectiveness of interventions. It is well accepted that a stenosis causing greater than 50% diameter reduction is considered to be a hemodynamically significant lesion. This value is based on both experimental modeling of flow stenosis[631] and correlation of thrombosis rates and degree of stenosis.[10] This value is based upon the physiology of a "critical arterial stenosis."[450,451] A 50% reduction in luminal diameter corresponds to a 75% reduction in cross-sectional area, the critical point at which blood flow begins to dramatically decrease.

Measuring technical success. What determines technical success for endovascular interventions? Should technical success be based upon anatomic criteria, the measurement of which is both subjective and fraught with error and usually not assessed in 2 orthogonal views? Or should it be based upon normalization of a hemodynamic

parameter that is less subjective and more reflective of vascular access performance? Possibilities include the use of flow measurements, static pressure, or ultrasound imaging during the PTA procedure or angioscopy after the procedure. Continued clinical investigation hopefully will provide scientific support for the use of hemodynamic end points, not anatomic end points.

Endovascular stents would seem to be an ideal method to treat angioplasty failures. Stents can oppose elastic recoil and optimize endoluminal dimensions, thereby improving intragraft blood flow and prolonging graft patency. However, the majority of clinical studies showed that the routine use of stents does not provide an additional benefit compared with angioplasty alone.[460,461] The neointimal hyperplastic tissue continues to grow unabated through the meshwork of the metallic stent. For these reasons, use of endovascular stents to treat HD-related stenoses continues to be a controversial subject. A recent study reported that use of nitinol stents provided superior results compared with stainless steel stents.[632] Continued improvements in stent design, the use of stent grafts, or the use of drug-eluting stents may provide better long-term results. Covered stents have been used to salvage AVGs, but efficacy has not been compared with other strategies.

Balloon sizing and selection. Balloons are now available in various sizes, have cutting edges, and are capable of delivering drugs. The proper selection and use of these balloons requires additional studies.

Mechanical thrombectomy devices. Comparative studies are needed on efficacy and cost. A reanalysis of existing data with differing devices should be performed.

Thrombolytics and anticoagulation. Although heparin typically is used during an endoluminal thrombectomy procedure, the proper role of thrombolytics is unknown. The spectrum has shifted from pharmacolytic to mechanical thrombectomy. Whether some lytics and their efficacy are superior to others in terms of outcomes is unknown. Several small series also suggested that dialysis within hours of thrombectomy influences patency.

Comparison of intervention methods. Do percutaneous and surgical techniques provide similar results or are we using percutaneous techniques simply because of the unavailability of surgical manpower for performing large numbers of vascular access–related procedures in an expedient manner? From another perspective, are we sacrificing long-term patency of the AVG to avoid insertion of an HD catheter?

Several reasonable studies reported that surgical techniques for AVG repair can provide substantially better outcomes compared with percutaneous techniques.[467,468,472] By establishing substantially higher primary patency goals after surgical repair, the KDOQI guidelines have acknowledged the superiority of surgical techniques. However, because of a variety of factors, including the unavailability of surgeons, the growth of interventional nephrology, the trend toward outpatient vascular access services, and the profitability of percutaneous procedures, the superiority of surgical techniques seems to have been forgotten.

Do surgical techniques for AVG repair provide more durable results with better long-term patency compared with percutaneous techniques? Is this a political issue, a manpower issue, or a financial issue?

Prevention of stenosis. This is a particularly important area. Both basic studies and pharmaceutical interventions are needed.

Guideline 7. Prevention and Treatment of Catheter and Port Complications

The ideal catheter diameter is not established. Are there concomitantly increased complications associated with larger diameter catheters?

Studies are needed to evaluate the risk versus benefit of higher dose warfarin therapy (INR $>$ 1.6) on catheter patency.

A comparison of lytic treatments is needed to examine:

- "Dwell" versus push versus infusion for catheters unable to deliver BFR of 300 mL/min
- Comparison of lytic agents for efficacy, cost, and long-term performance
- A number of studies on "anticoagulant locks" should be done in which primary outcome parameters of maintained access flow, resource use, and cost of care are evaluated. These include:
  1. Comparison of heparin at different concentrations (1,000 U and 5,000 U/mL) for all 3 dialysis sessions per week versus substitution of one of the heparin locks by tPA lock
  2. Use of high dose tPA (2.5–5 mg/lumen) where the catheter blood flow delivered at -250 mm Hg falls to $<$300 mL/min or decreases by 100 mL/min from its best flow ever

A definitive study should be performed to determine the natural history of catheter/port-related complications in the central veins, by using central venograms, that begins with de novo catheter placement, every 6-month follow-up, and with eachthe lowest rate in the last four decadescatheter complication (CRB, fibrin sheath, and all other types of catheter dysfunction).

Studies are needed to determine the association between infection and fibrin sheaths in catheters.

The optimal duration of antibiotic therapy for catheter-related infections should be examined.

Prospective studies are needed to examine antibiotic locks as an adjunct to save catheter versus "site salvage." Outcomes as primary and economics as secondary factors should be considered.

RESEARCH RECOMMENDATIONS OF INTEREST

Guideline 1. Patient Preparation for Permanent HD Access

Does patient education on the various risks/benefits of catheters versus fistulae/grafts alter success in placement? Is it an ethical study?

What demographic variables influence the likelihood of permanent access construction among a cohort of patients seen in a CKD clinic?

Guideline 2. Selection and Placement of HD Access

Studies are needed to determine the optimum duration of rest of a young (in use for <3 months) fistula after it has been infiltrated (ie, presence of hematoma with associated induration and edema). What parameters should be examined and how should such a study be designed?

The effects of catheter tip location on catheter or port catheter system performance should be studied—in the SVC/right atrium, common iliac, low IVC, and high IVC/right atrium. For the same French and luminal diameter, pressure flow curves should be performed keeping catheter design constant (ie, without mixing stepped and split catheters).

Studies are required to examine the effect of jets from catheter tips on central veins.

Guideline 3. Cannulation of Fistulae and Grafts and Accession of HD Catheters and Port Catheter Systems

What effect does correction of anemia have on access flow in fistulae? Prospective observational studies are needed.

Guideline 4. Detection of Access Dysfunction: Monitoring, Surveillance, and Diagnostic Testing

Research is needed on portable ultrasound devices for assessing flow easily and repetitively without operator effects.

Studies are needed to determine whether a properly performed DVP test retains any utility in detecting stenoses in fistulae.

Comparisons of surveillance techniques (access flow, DVP, P_{IA}) are required in fistulae using DDU anatomic imaging or contrast angiography to determine sensitivity and specificity. Low-end techniques (physical examination + derived P_{IA} ± flow achieved/prepump pressure) should be compared with high-end methods (Q_A by UDT or GPT alone ± flow by in-line dialysance, DDU).

Guideline 5. Treatment of Fistula Complications

Comparative trials are needed to examine interventional versus surgical modalities to correct maturation failure, with measurement of access flow longitudinally before and after correction.

Guideline 6. Treatment of AVG Complications

Treatment of infection. There are few informative data on the treatment of infected grafts. Decisions on using antibiotics, removal or not of the AVG, and duration of antibiotic use usually are made based on experimental considerations and recommendations from infectious disease consultants and CDC publications. Most of these recommendations are extrapolations and are not based on specific studies of dialysis patients with AVGs.

Arterial lesions and steal. In an increasingly older population with a greater incidence of diabetes, arterial lesions are not uncommon in patients undergoing vascular access constructions.[409] Steal occurs with high-flow fistulae. Prediction of its occurrence[80,633] and means to prevent its development[634] require prospective outcome studies. Once developed, several methods can be used to correct the problem,[411,431,433,635,636] but without consensus about the best procedure.[48,637] When distal digital ischemic changes or gangrene appear ipsilateral to a functioning graft, we need more studies to determine whether the problem is purely "ischemic" or perhaps embolic.[431,638]

Prediction of successful AVG function. A multitude of factors probably influence the longevity of AVG function,[143] including the individual's genetic predisposition for neointimal hyperplasia, surgical techniques, cannulation, and so on. These factors have not been systemically studied.

Guideline 7. Prevention and Treatment of Catheter and Port Complications

Studies should examine the value of sequential measurement of dialyzer flow rates and delivered and prepump arterial pressures during sequential dialysis treatments in detecting problems while they are still amenable to pharmacological or mechanical intervention. With modern catheters, what is the value of the conductance (BFR/arterial prepump pressure) in predicting catheter dysfunction?

Research is needed to define the optimum value of flow rate: 300 versus 350 mL/min if the initial flow is greater than 400 mL/min. Outcome parameters should include effects on adequacy, manpower utilization, and cost of intervention.

Studies should culture the tips of all catheters removed for both CRB and fibrin sheath disruption to determine the frequency of occult "silent" infection.

Additional studies are required to define the agents and concentrations of antibiotic locks that can be used, including studies of systemic levels during prolonged periods.

Long-term studies are needed on antibiotic and antimicrobial resistance to antibiotic locks and ointments used to prevent infection.

Work Group Biographies

Anatole Besarab, MD (Co-Chair), received his medical degree from the University of Pennsylvania, USA, and then carried out his internship and residency in medicine at Pennsylvania Hospital. Dr Besarab then spent 3 years as renal Fellow at Harvard Medical School (under Dr Frank Epstein) in Boston, MA, before moving to Thomas Jefferson University in Philadelphia, PA, for 19 years, followed by his first stint at Henry Ford Hospital, Detroit, MI. For 2 years he was Section Chief at West Virginia University. He currently is on the faculty of the Division of Nephrology and Hypertension at Henry Ford Hospital, and has his academic appointment at Wayne State University. In the past decade, Dr Besarab's work has focused on optimizing the management of anemia and detecting vascular access dysfunction before thrombosis. His current research interests include evaluation of diagnostic tests to detect angioaccess dysfunction and developing algorithms that maximize hematopoietic response to epoetin. He is author of more than 100 papers, 30 chapters, and several monographs and has spoken extensively at national meetings and academic centers. He has served on various committees for the Forum of ESRD Networks of End-Stage Renal Disease Networks, the American Society of Nephrology, ASAIO (American Society for Artificial Internal Organs), and the National Institutes of Health. He has served on the editorial board of several journals, reviews extensively for many journals, and is a reviewer for UpToDate. He is the current Chairman of the National Kidney Foundation Work Group on Vascular Access. Dr Besarab has received research funds, grants or contracts from Abbott Laboratories, Advanced Magnetics, Affymaz, American Regent Inc. Amgen, Inc., Baxter, Genentech, Hoffman-La Roche, Rockwell International, Transonic Systems Inc., VascAlert, and Watson Pharmaceuticals.

Deborah Brouwer, RN, CNN, is Director of Therapeutic and Clinical Programs at Renal Solutions, Inc. She is a member of the American Society of Diagnostic and Interventional Nephrology, the National Kidney Foundation Council of Nephrology Nurses and Technicians, and the American Nephrology of Nurses' Association. Ms Brouwer has received research funds, grants or contracts from CR Bard, Genentech, Transonic Systems Inc., and WL Gore.

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Lesley C. Dinwiddie, MSN, RN, FNP, CNN, is a self-employed nephrology nurse consultant. She is a member of the American Nephrology of Nurses' Association. Her areas of interest include vascular access, palliative care, and restless legs. She has received grants from ANNA, Genentech (and their medical education associates), Shire (including Cardinal MES and ProActive), American Regent, Ahrens, Balwit and Associates, Arrow,

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Stuart L. Goldstein, MD, is an Associate Professor of Pediatrics at the Baylor College of Medicine in Houston, TX. He is the Medical Director of the Dialysis Unit at the Texas Children's Hospital and the Administrative Director of the Pheresis Service at the Texas Children's Hospital, both of Houston. He is a member of the American Academy of Pediatrics, the American Society of Nephrology, the International Pediatric Nephrology Association, the American Society of Pediatric Nephrology, the International Society of Nephrology, and the Society for Pediatric Research. In addition, he is on the Medical Review Board for the End-Stage Renal Disease Network of Texas, Clinical Affairs Committee for the American Society of Pediatric Nephrology, Dialysis Advisory Group for the American Society of Nephrology, and Training/Certification Committee of the American Society of Pediatric Nephrology and is the Pediatric Nephrologist Representative for the International Society of Nephrology Commission of Acute Renal Failure. He has received grants from Gambro Renal Products; Dialysis Solutions, Inc; Baxter Healthcare; B. Braun, Inc; Amgen Inc; Abbott Laboratories; and Toray Inc. He also has lectured for Genentech. Dr Goldstein has received research funds, grants or contracts from the American Academy of Pediatrics, Baxter Healthcare, Dialysis Solutions, Inc., Gambro Renal Products, Genentech, Luitopold Pharmaceuticals, NxStage Inc., and the University of Missouri.

Mitchell L. Henry, MD, is Chief of the Division of Transplantation at Ohio State University. He is a member of the American Society of Transplant Surgeons. His areas of interest include transplantation, organ preservation, and immunosuppression. He has received grants from Novartis and MedImmune. Dr Henry has received research funds, grants or contracts from Coalescent/Medtronic, Genzyme, Novartis, Hoffman-La Roche, and Wyeth.

Klaus Konner, MD, is now a retired clinical nephrologist, dedicated particularly to the problems of vascular access, performing (as a nephrologist) access surgery during a period of 30 years, in addition to also practicing diagnostic and interventional radiology. He is a member of the European Dialysis and Transplant Association/European Renal Association, American Society of Nephrology, and a founding member of the Vascular Access Society. Dr Konner's special area of interest during the last decade is vascular access in elderly, hypertensive, and/or diabetic hemodialysis patients, aiming at a clear preference of the autologous arteriovenous fistula. He achieved more than 2,500 consecutive arteriovenous fistulae as a first-access procedure. Dr Konner has received research funds, grants or contracts from Gambro Renal Products, Germany.

Alan Lumsden, MD, FACS, is Professor and Chief of the Division of Vascular Surgery and Endovascular Therapy at the Baylor College of Medicine. He is a member of the Society of Vascular Surgery, the American Association for Vascular Surgery, the Society of Clinical Vascular Surgery, the International Society of Endovascular Specialists, the Association of Vascular Access Surgeons, the Peripheral Vascular Surgery Society, the International Society of Endovascular Specialists, the Texas Medical Association, the Michael E. DeBakey International Surgical Society, the Harris County Medical Society, the San Antonio Vascular

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Jack Work, MD (Co-Chair), is Professor of Medicine and Director of Interventional Nephrology at Emory University. He is the chairperson of the End-Stage Renal Disease Clinical Performance Measures QI Vascular Access Committee, a member of the National Vascular Access Improvement Initiative and Leadership group, and a member of CMS Dialysis Facility Compare Vascular Access Quality Expert panel. He currently is president of the American Society of Diagnostic and Interventional Nephrology and a board member of the Vascular Access Society of the Americas. His areas of interest include vascular access management, the biology of neointimal hyperplasia, vascular access surveillance techniques, and continuous flow peritoneal dialysis. Dr Work has received research funds, grants or contracts from Cleveland Clinic, National Kidney Foundation's Clinical Meeting, Novoste Corporation, the University of Missouri Dialysis Conference, and Vasca Inc.

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Acronyms and Abbreviations

AVF	Arteriovenous fistula
AVG	Arteriovenous graft
BP	Blood pressure
CHF	Congestive heart failure
CPR	Clinical Practice Recommendations
CrCl	Creatinine clearance
CVD	Cardiovascular disease
DOQI	Dialysis Outcomes Quality Initiative
GFR	Glomerular filtration rate
HD	Hemodialysis
HTN	Hypertension
KDOQI	Kidney Disease Outcomes Quality Initiative
Kt/V	Measure of dialysis adequacy calculated from K (dialyzer clearance), t (time) and V (volume of body water in a given patient)
LVH	Left ventricular hypertrophy
NKF	National Kidney Foundation
PD	Peritoneal dialysis
RCT	Randomized controlled trial
ROC	Receiver operating characteristics
SGA	Subjective global assessment
TPA	Tissue plasminogen activator
UOP	Urine output
UrCl	Urea clearance
US	Ultrasonography

APPENDIX 1. METHODS FOR EVALUATING EVIDENCE

AIM

The overall aim of the project was to update the 2000 Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guidelines on Hemodialysis and Peritoneal Dialysis Adequacy, and Vascular Access. The Work Group sought to update the guidelines using an evidence-based approach. After topics and relevant clinical questions were identified for the updates, the available scientific literature on those topics was systematically searched and summarized.

OVERVIEW OF PROCESS

Update of the guidelines required many concurrent steps to:

- Form the Work Groups and Evidence Review Team that were to be responsible for different aspects of the process;
- Confer to discuss process, methods, and results;
- Develop and refine topics;
- Define exact populations of interest;
- Create draft guideline statements and rationales;
- Create data extraction forms;
- Create and standardize quality assessment and applicability metrics;
- Develop and perform literature search strategies;
- Screen abstracts and retrieve full articles;
- Review articles;
- Extract data and perform critical appraisal of the literature;
- Tabulate data from articles into summary tables;
- Write guideline statements and rationales based on literature and Work Group consensus.

Separate Work Groups were created for each subject area: hemodialysis adequacy, peritoneal dialysis adequacy, and vascular access. The 3 groups worked in parallel to create the guidelines. The Work Group Chairs conferred regarding overlapping topics across guidelines. The Evidence Review Team, comprised of experts in systematic review and guideline development, guided the Work Groups in all methods and aspects of guideline development.

Creation of Groups

The KDOQI Advisory Board selected the Work Group Chairs and the Director of the Evidence Review Team then assembled groups to be responsible for the development of the updates. These Work Groups and the Evidence Review Team collaborated closely throughout the project.

The Work Groups consisted of domain experts, including individuals with expertise in nephrology, surgery, radiology, pediatrics, nursing and nutrition. For each guideline

update, the first task of the Work Group members was to define the overall topics and goals of the updates. They then further developed and refined each topic, literature search strategies, and data extraction forms (described below). The Work Group members were the principal reviewers of the literature, and from their reviews and detailed data extractions, they summarized the available evidence and took the primary roles of writing the guidelines and rationale statements. Completed data extractions were posted on a National Kidney Foundation (NKF) website for direct access by Work Group members.

The Evidence Review Team consisted of nephrologists (1 senior nephrologist and 2 nephrology fellows), methodologists, and research assistants from Tufts-New England Medical Center with expertise in systematic review of the medical literature. They instructed the Work Group members in all steps of systematic review and critical literature appraisal. The Evidence Review Team also coordinated the methodological and analytical process of the report, defined and standardized the methodology of performing literature searches, of data extraction, and of summarizing the evidence in summary tables. They organized abstract and article screening, created forms to extract relevant data from articles, organized Work Group member data extraction, and tabulated results. Throughout the project the Evidence Review Team led discussions on systematic review, literature searches, data extraction, assessment of quality and applicability of articles, evidence synthesis, and grading of the quality of the body of evidence and the strength of guideline recommendations.

Refinement of Update Topics and Development of Materials

The Work Group reviewed the 1995 Dialysis Outcomes Quality Initiative (DOQI) Clinical Practice Guidelines and the 2000 KDOQI updates and decided which of the guideline recommendations required updates and which should remain unchanged. These assessments were based primarily on expert opinion regarding the currency of the previous guidelines and the likelihood of availability of new evidence. Preliminary literature searches were made to inform this process. To allow for timely review, it was determined that each set of guidelines would be able to have systematic reviews on only a limited number of topics. After literature review, the experts decided which recommendations would be supported by evidence or by opinion. As described below, recommendations based on adequate evidence were categorized as Guidelines (CPGs), while opinion-based statements were categorized as Clinical Practice Recommendations (CPRs).

The Work Groups and Evidence Review Team developed: a) draft guideline statements; b) draft rationale statements that summarized the expected pertinent evidence; and c) data extraction forms containing the data elements to be retrieved from the primary articles. The topic refinement process began prior to literature retrieval and continued through the process of reviewing individual articles.

Literature Search

Based on the draft guideline statements, the Work Group members agreed on topics that would be systematically reviewed and formulated questions defining predictors, interventions, comparators, and outcomes of interest. Search strategies were developed based

on these questions and topics, in addition to the study designs and years of publications of interest to the Work Group. Articles of interest were identified through MEDLINE searches of English language literature of human studies in May through July 2004. Broad search terms were used to avoid missing potentially pertinent articles. The searches were supplemented by articles identified by Work Group members through June 2005.

Only full journal articles of original data were included. The searches were limited to studies published since January 1997 since earlier publications were reviewed in the previous DOQI guidelines. Editorials, letters, abstracts, and unpublished reports were not included. Selected review articles, however, were included for background material. No systematic process was followed to obtain review articles.

Abstracts and titles from the MEDLINE search results were prescreened by members of the Evidence Review Team for general relevance. A second round of screening was performed on the abstracts by Work Group members for relevance using predefined eligibility criteria, described below. Articles were retrieved by the Evidence Review Team and then rescreened by Work Group members and/or the Evidence Review Team. Eligible studies were extracted using standardized extraction forms. Domain experts made the final decisions regarding the eligibility of all articles.

Generation of Data Extraction Forms

Data extraction forms were designed to capture information on various aspects of the primary articles. Forms for all topics included study setting and demographics, eligibility criteria, causes of kidney disease, numbers of subjects, study design, study funding source, dialysis characteristics, comorbid conditions, descriptions of relevant risk factors or interventions, description of outcomes, statistical methods, results, study quality (based on criteria appropriate for each study design (see below), study applicability (see below), and sections for comments and assessment of biases. Training of the Work Group members to extract data from primary articles occurred by emails and teleconferences. Work Group members were assigned the task of data extraction of articles.

Generation of Evidence Tables

The Evidence Review Team condensed the information from the data extraction forms into evidence tables, which summarized individual studies. These tables were created for the Work Group members to assist them with review of the evidence and are not included in the guidelines. All Work Group members (within each Update) received copies of all extracted articles and all evidence tables. During the development of the evidence tables, the Evidence Review Team checked the data extraction for accuracy and rescreened the accepted articles to verify that each of them met the initial screening criteria determined by the Work Group. If the criteria were not met, the article was rejected, in consultation with the Work Group.

Format for Summary Tables

Summary Tables describe the studies according to the following dimensions: study size and follow-up duration, applicability or generalizability, results, and methodological quality. Within each table, the studies are first grouped by outcome type.

Data entered into Summary Tables were derived from the data extraction forms, evidence tables, and/or the articles by the Evidence Review Team. All Summary Tables were reviewed by the Work Group members.

Within each outcome, studies are ordered first by methodological quality (best to worst), then by applicability (most to least), and then by study size (largest to smallest). When relevant, outcome thresholds (eg, of access flow measurement) are included. Results are presented by using the appropriate metric or summary symbols, as defined in the table footnotes.

Systematic Review Topics, Study Eligibility Criteria, and Studies Evaluated

The topics for each Update were selected by the respective Work Group members for systematic review (Table 1, Table 2, Table 3). The eligibility criteria were defined by the Work Group members of each Update in conjunction with the Evidence Review Team.

Literature Yield for Hemodialysis Adequacy (Table 4)

A total of 2,526 citations were screened, of which 319 were review articles and 14 were added by Work Group members. There were 223 articles (191 studies in adults and 32 in children) that were potentially relevant. These articles were retrieved for full review. Of these, 87 adult articles were accepted for full data extraction by the Work Group members. Eight articles in children were formally data extracted by a pediatric nephrologist on the Work Group. Articles in adults were randomly assigned to individual Work Group members for data extraction. Of these, 23 studies answered questions pertinent to topics chosen for systematic listing in Summary Tables.

Literature Yield for Peritoneal Dialysis Adequacy (Table 4)

A total of 2,307 citations were screened and 7 were added by Work Group members. There were 293 articles (263 studies in adults and 30 in children) that were potentially relevant. These articles were retrieved for full review. Of these, 101 adult articles were accepted for full data extraction by the Work Group members. Nine articles in children were formally data extracted by a pediatric nephrologist on the Work Group. Articles in adults were randomly assigned to individual Work Group members for data extraction. Of these, 27 studies answered questions pertinent to topics chosen for systematic listing in Summary Tables.

Literature Yield for Vascular Access (Table 4)

A total of 2,892 citations were screened, of which 388 were review articles. There were 112 articles (89 studies in adults, 13 in children, 10 review articles) that were potentially relevant. These articles were retrieved for full review. Of these, 58 articles were accepted for full data extraction by the Work Group members. Because of small sample sizes, articles in children were not formally data extracted but reviewed in detail by the 2 pediatric nephrologists on the Work Group and used to write the narrative summary in the pediatric section. Articles in adults were randomly assigned to individual Work Group members for data extraction. Five additional articles were added by Work Group experts and the Evidence Review Team. Finally, 24 studies answered questions pertinent to topics chosen for systematic listing in Summary Tables.

Search terms for all updates are shown in Appendix 2.

Table 1. Topics and Eligibility Criteria for Systematic Review: Hemodialysis Adequacy, Update 2006

Topic 1 (guideline 6)	**What is the role of residual kidney function compared to dialysis dose for clinical outcomes, including hospitalization and mortality?**
Population	Patients on HD
Predictor/Intervention	Direct comparisons of dialysis dose versus residual kidney function
	Direct comparisons of including or excluding residual kidney function in calculating dialysis dose
Outcomes	Clinical outcomes (death, hospitalization, CVD/CHF events, other events)
Screening Criteria	Minimum duration: 6 months
	Any study design (prospective or retrospective)
Topic 2 (guideline 4)	**What should be the recommended minimum dose for adequate dialysis using urea kinetics? Should separate goals be set for specific subgroups of patients such as race, gender, age or residual kidney function?**
Population	Patients on HD
Predictor/Intervention	Kt/V
Outcomes	Clinical outcomes (death, hospitalization, CVD/CHF events, other events)
Screening Criteria	Minimum duration: 6 months
	Any study design (prospective or retrospective)
Topic 3 (guideline 5)	**Does the use of a particular type of dialyzer reuse (or lack of reuse) have either an adverse or beneficial effect on either intermediate outcomes or mortality? Are these benefits seen only in specific subgroups of patients, such as race, gender, age, or residual kidney function?**
Population	Patients on HD
Predictor/Intervention	Dialyzer reuse or lack of reuse, and method of "cleaning" for reuse
Outcomes	Clinical outcomes (death, hospitalization, CVD/CHF events, other events)
	Adverse events (allergy, toxicity, etc.)
	Intermediate outcomes (clearance and filtration measures)
Screening Criteria	Clinical Outcomes
	Minimum follow-up 6 months; Direct comparisons only; Prospective or retrospective
	Adverse events
	No minimum follow-up; Any study design
	Intermediate outcomes
	No minimum follow-up; Direct comparisons only; Prospective or retrospective

Grading of Individual Studies

Study Size and Duration

The study (sample) size is used as a measure of the weight of the evidence. In general, large studies provide more precise estimates of prevalence and associations. In addition, large studies are more likely to be generalizable; however, large size alone, does not guarantee applicability. A study that enrolled a large number of selected patients may be less generalizable than several smaller studies that included a broad spectrum of patient populations. Similarly, longer duration studies may be of better quality and more applicable, depending on other factors.

Applicability

Applicability (also known as generalizability or external validity) addresses the issue of whether the study population is sufficiently broad so that the results can be generalized

Table 2. Topics and Eligibility Criteria for Systematic Review: Peritoneal Dialysis Adequacy, Update 2006

Topic 1 (guideline 2)	**What is the association between achieved (or target) clearance values and clinical outcomes?**
Population	Patients on PD
Predictor/Intervention	Clearance measured as achieved total Kt/V (including residual kidney function), CrCl, or prescription (dialysis dose)
Outcomes	Clinical outcomes = death, hospitalization, technique survival, nutrition (albumin, SGA, possibly others), growth (pediatrics), cognitive (pediatrics), allowed other pediatric outcomes
Screening Criteria	Study design: Longitudinal cohorts and RCTs Minimum Duration: Death, Hospitalization/Technique survival 1 year; Others 1 month
Topic 2 (guideline 2)	**What is the association between achieved (or target) level of fluid/Na removal parameters and clinical outcomes?**
Population	Patients on PD
Predictor/Intervention	Net fluid/volume removal (+/-residual kidney function) Net sodium removal (including dietary Na restriction) Ultrafiltration volume; Volume status; Blood pressure
Outcomes	Clinical outcomes: death, hospitalization, technique survival, nutrition (albumin, SGA, possibly others), growth (pediatrics), cognitive (pediatrics), allowed other pediatric outcomes, BP/HTN, LVH
Screening Criteria	Study design: Longitudinal cohort studies (RCTs if available) No minimum study duration (except >= 1 year for mortality) Search 1999-2004
Topic 3 (guideline 3)	**What treatments are effective to preserve residual kidney function and maximize urine output? Among studies that answer this question, is there evidence that the treatments affect clinical outcomes?**
Population	Patients on PD
Predictor/Intervention	Pharmacological interventions
Outcomes	Kidney: Residual kidney function for solute clearance (GFR from UrCl and CrCl), salt and water excretion (UOP) Clinical: death, hospitalization, technique survival, growth (pediatrics), cognitive (pediatrics), allowed other pediatric outcomes
Screening Criteria	Study design: Direct comparisons only (either RCT, uncontrolled parallel comparison, observational single cohort cross-over (from solution A to solution B, no minimum washout period) Minimum study duration: shorter for residual kidney function and longer for clinical outcomes (determine exact thresholds upon reviewing available studies) Search: 2000-2004

to the population of interest at large. The study population is typically defined primarily by the inclusion and exclusion criteria. The target population was defined to include patients with kidney failure, specifically those on dialysis. A designation for applicability was assigned to each article, according to a three-level scale. In making this assessment, sociodemographic characteristics were considered, as well as comorbid conditions and prior treatments. Applicability is graded in reference to the population of interest as defined in the clinical question. For example for the question of treatment of catheter-related infections the reference population is that of HD patients with infected cuffed tunneled HD catheters.

Sample is representative of the target population, or results are definitely applicable to the target population irrespective of study sample.

Table 3. Topics and Eligibility Criteria for Systematic Review: Vascular Access, Update 2006

Topic 1 (guideline 1)		**Effectiveness of preoperative venous imaging/mapping for planning AVF construction**
	Population	Patients on HD or for future HD, undergoing imaging study in preparation for AVF construction
	Predictor/Intervention	Duplex US
	Outcomes	Maturation and function of new AVF, as defined in study (If several outcomes were reported, the following were extracted: successful use for first dialysis and delivery of adequate dialysis dose for at least 1 month) Change in approach to access placement
	Screening Criteria	Longitudinal studies, prospective or retrospective, including before / after comparisons, any duration Exclude studies of feasibility or diagnostic accuracy (sensitivity/specificity) Exclude studies with venograms as predictor
Topic 2.1 (guideline 7)		**Treatment of catheter-related infection and the use of antibiotic locks**
	Population	HD patient with cuffed, tunneled HD catheter and catheter-related infection, as defined by the Centers for Disease Control and Prevention, including bacteremia
	Predictor/Intervention	Catheter removal versus no catheter removal with or without use of antibiotic locks Different methods of removal; Different durations of line holiday prior to reinsertion
	Outcomes	Infection clearing rates; Reinfection rates
	Screening Criteria	Prospective controlled trials of any duration
Topic 2.2 (guideline 7)		**Prophylaxis of catheter-related infection and the use of antibiotic locks**
	Population	HD patient with cuffed, tunneled HD catheter without current catheter-related infection
	Predictor/Intervention	Prophylaxis with "antibiotic lock" (mixture of antibiotic and coagulant planted intra-catheter)
	Outcomes	Infection free time; Catheter survival; Infection rate/1000 patient days
	Screening Criteria	Prospective controlled trials Minimum 1000 days at risk (total)
Topic 3.1 (guideline 7)		**Treatment of malfunctioning cuffed tunneled HD catheter with thrombolytics**
	Population	HD patient with cuffed, tunneled HD catheter, which is malfunctioning.
	Predictor/Intervention	Treatment with: TPA; Reteplase (Retavase); Urokinase; Other investigational agents in phase 3 studies; Any methods of fibrin sheath stripping (including continuous infusion, catheter exchange, angioplasty)
	Outcomes	Re-establishment of patency/function, ability to restart HD treatment, access survival
	Screening Criteria	Prospective controlled trials of any duration Only cuffed/tunneled catheters, not uncuffed For fibrin sheath stripping studies, only those with radiographic evidence of fibrin sheath Exclude studies using streptokinase
Topic 3.2 (guideline 7)		**Prophylaxis of cuffed tunneled HD catheter malfunctioning with thrombolytics**
	Population	HD patient with functional cuffed, tunneled HD catheter
	Predictor/Intervention	Prophylaxis with: TPA; Reteplase (Retavase); Urokinase; Other investigational agents in phase 3 studies; Any methods of fibrin sheath stripping (including continuous infusion, catheter exchange, angioplasty)
	Outcomes	Maintenance of patency/function, blood flow achieved, access survival
	Screening Criteria	Prospective controlled trials Minimum 1000 days at risk Only cuffed/tunneled catheters, not uncuffed Exclude studies using streptokinase
Topic 4 (guideline 4)		**Performance of different techniques for access surveillance and efficacy of periodic access monitoring for prolonging access life and maintaining access function**
4.1		**How do different tests compare to each other?**
	Population	HD patient with functional AVFs or AVGs
	Predictor/Intervention	Diagnostic test studies comparing performance of one technique of measuring access function with another reference test
	Outcomes	Sensitivity, specificity ROC curves
	Screening Criteria	Cross-sectional diagnostic test studies
4.2		**How do different methods of access surveillance compare for predicting access clotting?**
4.3		**How should one act on abnormal test results to prevent access clotting?**
	Population	HD patient with functional AVFs or AVGs
	Predictor/Intervention	Periodic access surveillance by physical exam or other methods which measure access flow Static pressures; Dynamic pressures; Recirculation; Flow/other parameters
	Outcomes	Maintenance of function; Maintenance of patency; or access survival; Exclude studies only reporting blood flow

Table 4. Literature Search and Review by Topic

Guideline Topic	Citations Screened	Articles Retrieved	Articles Added by Experts	Articles Data-Extracted*	Articles Included in Summary Tables*
Hemodialysis	2,512	223	14	87	23
1			0	31	0
2			0	5	2
3			0	19	11
4			0	27	10
5			0	7	1
Peritoneal Dialysis	2,300	293	7	101	27
1			0	28	17
2			0	21	4
3			0	12	4
4			0	26	1
5.1			0	17	5
5.2			0	8	0
Vascular Access	2,892	112	5	58	24
1			0	10	0
2.1			0	2	0
2.2			0	4	3
3.1			0	6	2
3.2			0	3	3
4.1			0	10	9
4.2			2	17	4
4.3			3	7	4

*Columns do not add up because some studies were data-extracted for more than 1 topic and used in more than 1 Summary Table.

Sample is representative of a relevant sub-group of the target population. For example, sample is only representative of people with virgin arteriovenous fistulas, or only a specific relevant subgroup, such as elderly individuals or incident dialysis patients.

Sample is representative of a narrow subgroup of patients only, and not well generalizable to other subgroups. For example, the study includes only a small number of patients or patients with a rare disease or virgin fistulas with no access dysfunction. Studies of such narrow subgroups may be extremely valuable for demonstrating exceptions to the rule.

Results

The type of results available in each study is determined by the study design, the purpose of the study, and the question(s) being asked. The Work Group decided on the eligibility criteria and outcomes of interest (see Tables 1-3).

Diagnostic Test Studies

For studies of diagnostic tests, sensitivity and specificity data or area under the curve were included when reported. When necessary, sensitivity and specificity data were calculated from the reported data. Diagnostic tests were evaluated according to a hierarchy

of diagnostic tests.* Each test was assessed according to diagnostic technical capacity, accuracy, diagnostic and therapeutic impact, and patient outcome. This ultimately affected the overall strength of a recommendation regarding a diagnostic test.

Methodological Quality

Methodological quality (or internal validity) refers to the design, conduct, and reporting of the clinical study. Because studies with a variety of types of design were evaluated, a 3-level classification of study quality was devised:

- ● Least bias; results are valid. A study that mostly adheres to the commonly held concepts of high quality, including the following: a formal study; clear description of the population and setting; clear description of an appropriate reference standard; proper measurement techniques; appropriate statistical and analytical methods; no reporting errors; and no obvious bias. Not retrospective studies or case series.
- ◉ Susceptible to some bias, but not sufficient to invalidate the results. A study that does not meet all the criteria in the category above. It has some deficiencies but none likely to cause major bias.
- ○ Significant bias that may invalidate the results. A study with serious errors in design or reporting. These studies may have large amounts of missing information or discrepancies in reporting.

Summarizing Reviews and Selected Original Articles

Work Group members had wide latitude in summarizing reviews and selected original articles for topics that were determined not to require a systemic review of the literature.

Guideline Format

The format for each guideline chapter is outlined in Table 5. Each guideline contains 1 or more specific "guideline statements" that represent recommendations to the target audience. Each guideline contains background information, which is generally sufficient to interpret the guideline. The rationale for each guideline describes the evidence upon which each guideline recommendation is based. The guideline concludes with a discussion of limitations of the evidence review and a brief discussion of clinical applications, and implementation issues regarding the topic. Research recommendations for each guideline update are summarized in a separate section at the end of each guideline update.

Rating the Strength of Recommendations

After literature review, the experts decided which recommendations were supported by evidence and which were supported by consensus of Work Group opinion. Evidence-based guideline recommendations were graded as strong (A) or moderate (B). Recommendations based on weak evidence (C) and/or consensus of expert opinion were labeled as Clinical Practice Recommendations (CPRs). An "A" rating indicates "it is strongly recommended that clinicians routinely follow the guideline for eligible patients. There is

*Fineberg HV, Bauman R, Sosman M: Computerized cranial tomography. Effect on diagnostic and therapeutic plans. JAMA 238:224-227, 1977

Table 5. Format for Guidelines

Introductory Statement
Guideline or CPR Statement 1
Guideline or CPR Statement 2
BACKGROUND
RATIONALE
Definitions (if appropriate)
Rationale statement 1
Supporting text and tables
Rationale statement 2
Supporting text and tables
LIMITATIONS
IMPLEMENTATION ISSUES

Research Recommendations are presented in a separate chapter.

strong evidence that the practice improves health outcomes, and benefits substantially outweigh harm." The "B" rating indicates "it is recommended that clinicians routinely follow the guideline for eligible patients. There is moderately strong evidence that the practice improves health outcomes." A "CPR" rating indicates "it is recommended that clinicians consider following the guideline for eligible patients. This recommendation is predominantly based on consensus of opinions of the Work Group and reviewers that the practice might improve health outcomes." (See Table 6).

The strength of each guideline recommendation is based on the quality of the supporting evidence as well as additional considerations. Additional considerations, such as cost, feasibility, and incremental benefit were implicitly considered. The quality of evidence was not explicitly graded. It was implicitly assessed according to the criteria outlined in Table 7, and considered: i) the methodological quality of the studies; ii) whether

Table 6. Rating the Strength of Guideline Recommendations

Grade	Recommendation
A	It is strongly recommended that clinicians routinely follow the guideline for eligible patients. There is strong evidence that the practice improves health outcomes.
B	It is recommended that clinicians routinely follow the guideline for eligible patients. There is moderately strong evidence that the practice improves health outcomes.
CPR	It is recommended that clinicians consider following the guideline for eligible patients. This recommendation is based on either weak evidence or on the opinions of the Work Group and reviewers that the practice might improve health outcomes.

Health outcomes are health-related events, conditions, or symptoms that can be perceived by individuals to have an important effect on their lives. Improving health outcomes implies that benefits outweigh any adverse effects.

Table 7. Rating the Quality of Evidence

Outcome	Population	Methodological Quality: Well designed and analyzed (little, if any, potential bias)	Some problems in design and/or analysis (some potential bias)	Poorly designed and/or analyzed (large potential bias)
Health outcome(s)	Target population	Strong[a]	Moderately strong[b]	Weak[c]
Health outcome(s)	Other than the target population	Moderately strong[d]	Moderately strong[e]	Weak[f]
Surrogate measure for health outcome(s)	Target population	Moderately strong[g]	Weak[h]	Weak[i]
Surrogate measure for health outcome(s)	Other than the target population	Weak[j]	Weak[k]	Weak[l,m]

Strong- [a]Evidence includes results from well-designed, well-conducted study/studies in the target population that directly assess effects on health outcomes.
Moderately strong- [b]Evidence is sufficient to determine effects on health outcomes in the target population, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies; [d]R evidence is from a population other than the target population, but from well-designed, well-conducted studies; [e]R evidence is from studies with some problems in design and/or analysis; [g]R evidence is from well-designed, well-conducted studies on surrogate endpoints for efficacy and/or safety in the target population.
Weak- [c]Evidence is insufficient to assess the effects on net health outcomes because it is from studies with some problems in design and/or analysis on surrogate endpoints for efficacy and/or safety in the target population; [f]R the evidence is only for surrogate measures in a population other than the target population; [i]R the evidence is from studies that are poorly designed and/or analyzed.

or not the studies were carried out in the target population, ie, patients on dialysis, or in other populations; and iii) whether the studies examined health outcomes directly, or examined surrogate measures for those outcomes, eg, blood flow instead of access survival.

Limitations of Approach

While the literature searches were intended to be comprehensive, they were not exhaustive. MEDLINE was the only database searched, and searches were limited to English language publications. Hand searches of journals were not performed, and review articles and textbook chapters were not systematically searched. However, important studies known to the domain experts that were missed by the literature search were included in the review.

Because of resource limitations and other practical considerations, there were several deviations from the original protocol for several of the update topics. These primarily resulted in nephrologists in the Evidence Review Team, rather than Work Group members, performing the primary article screening and the data extraction for articles included in several Summary Tables. However, all articles that met criteria for all topics, all completed data extraction forms, and all Summary Tables were distributed to relevant Work Group members for critical review and incorporation into guidelines.

APPENDIX 2. MEDLINE SEARCH STRATEGIES

HEMODIALYSIS ADEQUACY, UPDATE 2006

Ovid MEDLINE, Ovid MEDLINE Daily Update, Ovid MEDLINE In-Process
Search from 1/1/97 through 6/22/04

#	Search History	Results
1	exp Renal Dialysis/	19447
2	HD.mp.	10309
3	hemodialysis.mp.	2737
4	or/1-3	22540
5	equilibrate$.mp.	1478
6	pool.mp.	15057
7	ionic dialysance.mp.	28
8	urea reduct$.mp.	176
9	flux.mp.	11892
10	urea kinetic$.mp.	230
11	dialysis adequacy.mp.	299
12	recirculation.mp.	1314
13	clearance.mp.	27570
14	kt.af.	2305
15	"dialysis dose".af.	299
16	"dialyzer membrane".af.	77
17	"dialyzer reuse".af.	42
18	conductance.af.	13812
19	pump.af.	16174
20	"residual renal function".af.	427
21	cellulose.af.	7347
22	synthetic.af.	45739
23	or/5-22	138437
24	4 and 23	3474
25	limit 24 to (human and English language and yr="1997-2004") [Limit not valid in: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations; records were retained]	2747
26	limit 25 to (addresses or bibliography or biography or case reports or congresses or consensus development conference or consensus development conference, nih or dictionary or directory or editorial or festschrift or government publications or interview or lectures or legal cases or legislation or letter or news or newspaper article or patient education handout or periodical index) [Limit not valid in: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations; records were retained]	235
27	25 not 25	2512
28	limit 27 to (guideline or meta analysis or practice guideline or review or review, academic or review literature or review, multicase or review of reported cases or review, tutorial)	319
29	27 not 28	2193

Ovid MEDLINE, Ovid MEDLINE Daily Update, Ovid MEDLINE In-Process
Search from 1/1/97 through 10/27/04 (search from 6/22/04 with "Artificial Kidney" added)

#	Search History	Results
1	exp Renal Dialysis/	20552
2	HD.mp.	10819
3	haemodialysis.mp.	2835
4	"Kidney, Artificial"/	215
5	or/1-4	23751
6	equilibrate$.mp.	1535
7	pool.mp.	15700
8	ionic dialysance.mp.	29
9	urea reduct$.mp.	184
10	flux.mp.	12080
11	urea kinetic$.mp.	235
12	dialysis adequacy.mp.	314
13	recirculation.mp.	1363
14	clearance.mp.	28747
15	kt.af.	2411
16	"dialysis dose".af.	321
17	"dialyzer membrane".af.	81
18	"dialyzer reuse".af.	44
19	conductance.af.	14164
20	pump.af.	16882
21	"residual renal function".af.	442
22	cellulose.af.	7628
23	synthetic.af.	47675
24	or/6-23	143780
25	5 and 24	3642
26	(20040728$ or 20040729$ or 20040630$).ed.	205970
27	25 not 26	3487
28	limit 27 to (human and English language and yr="1997-2004") [Limit not valid in: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations; records were retained]	2755
29	limit 28 to (addresses or bibliography or biography or case reports or congresses or consensus development conference or consensus development conference, nih or dictionary or directory or editorial or festschrift or government publications or interview or lectures or legal cases or legislation or letter or news or newspaper article or patient education handout or periodical index)	237
30	28 not 29	2518
31	limit 30 to (guideline or meta analysis or practice guideline or review or review, academic or review literature or review, multicase or review of reported cases or review, tutorial)	324
32	30 not 31	2194

PERITONEAL DIALYSIS ADEQUACY, UPDATE 2006

Ovid MEDLINE, Ovid MEDLINE Daily Update, Ovid MEDLINE In-Process. Search from 1/1/97 through 5/28/04

#	Search History	Results
1	exp PD/ and PD.mp.	13610
2	exp ultrafiltration/ and ultrafiltration.mp.	6801
3	or/1-2	20002
4	clearance.mp.	75604
5	exp urea/ or urea.mp.	88704
6	fluid removal.mp.	373
7	sodium removal.mp.	129
8	exp dialysis solutions/ or dialysis solution.mp.	3203
9	icodextrin.mp.	196
10	peritoneal membrane.mp. [mp=ti, ot, ab, rw, sh]	664
11	or/4-10	164459
12	limit 11 to yr=1989-2004	93187
13	residual renal function.mp.	618
14	peritoneal equilibration test.mp.	283
15	or/13-14	868
16	limit 15 to yr=2000-2004	334
17	3 and 12	2938
18	3 and 16	222
19	17 or 18	2999
20	limit 19 to (human and English language) [Limit not valid in: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations; records were retained]	2498
21	limit 20 to (addresses or bibliography or biography or case reports or congresses or consensus development conference or consensus development conference, nih or dictionary or directory or editorial or festschrift or government publications or interview or lectures or legal cases or legislation or letter or news or newspaper article or patient education handout or periodical index) [Limit not valid in: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations; records were retained]	223
22	20 not 21	2275
23	limit 21 to (guideline or meta analysis or practice guideline or review or review, academic or review literature or review, multicase or review of reported cases or review, tutorial)	25

VASCULAR ACCESS, UPDATE 2006

Search #1. Ovid MEDLINE, Ovid MEDLINE Daily Update, Ovid MEDLINE In-Process. Search from 1/1/97 through 5/5/04

#	Search History	Results
1	exp Renal Dialysis/	19138
2	HD.mp.	10126
3	exp Kidney Diseases/ or exp Kidney Failure, Chronic/	68052
4	exp Catheters, Indwelling/	3871
5	exp Catheterization, Central Venous/	3330
6	exp Vascular Fistula/	2369
7	exp Arteriovenous Fistula/	1637
8	vascular access.mp	1389
9	fistula.mp.	10910
10	catheter$.tw.	34890
11	or/1-3	77948
12	or/4-10	48299
13	11 and 12	3513
14	limit 13 to human [Limit not valid in: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations; records were retained]	3376
15	limit 14 to English language	2914
16	limit 15 to yr=1997-2004	2620
17	limit 16 to (addresses or bibliography or biography or case reports or congresses or consensus development conference or consensus development conference, nih or dictionary or directory or editorial or festschrift or government publications or interview or lectures or legal cases or legislation or letter or news or newspaper article or patient education handout or periodical index) [Limit not valid in: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations; records were retained]	694
18	16 not 17	1926
19	limit 18 to (guideline or meta analysis or practice guideline or review or review, academic or review literature or review, multicase or review of reported cases or review, tutorial)	338
20	18 not 19	1588

VASCULAR ACCESS, UPDATE 2006 PEDIATRIC SEARCH[a]

Ovid MEDLINE <1996 to July Week 3 2004>

Search from 1/1/97 through 7/28/04

#	Search History	Results
1	exp Renal Dialysis/	19635
2	HD.mp.	9798
3	exp Kidney Diseases/ or exp Kidney Failure, Chronic/	70022
4	exp Catheters, Indwelling/	3963
5	exp Catheterization, Central Venous/	3437
6	exp Vascular Fistula/	2443
7	exp Arteriovenous Fistula/	1678
8	vascular access.mp.	1352
9	fistula.mp.	10692
10	catheter$.tw.	34022
11	or/1-3	79524
12	or/4-10	47279
13	11 and 12	3549
14	limit 13 to human	3408
15	limit 14 to English language	2939
16	limit 15 to yr=1997-2004	2646
17	limit 16 to (addresses or bibliography or biography or case reports or congresses or consensus development conference or consensus development conference, nih or dictionary or directory or editorial or festschrift or government publications or interview or lectures or legal cases or legislation or letter or news or newspaper article or patient education handout or periodical index)	717
18	16 not 17	1929
19	limit 18 to (guideline or meta analysis or practice guideline or review or review, academic or review literature or review, multicase or review of reported cases or review, tutorial)	351
20	18 not 19	1578
21	limit 20 to ("infant (1 to 23 months)" or "preschool child (2 to 5 years)" or "child (5 to 12 years)" or "adolescent (13 to 18 years)")	292
22	20 not 21	1286
23	limit 22 to ("all adult (19 plus years)" or "newborn infant (birth to 1 month)")	918
24	20 not 23	660
25	20 not (21 or 23)	368

a. This search is a subset of search #1

VASCULAR ACCESS, UPDATE 2006 SEARCH #2

Ovid MEDLINE <1966 to August Week 2 2004>

Search from 1/1/97 through 8/19/2004 (original search date 5/5/04 with terms "shunt" and "graft" added)

#	Search History	Results
1	exp Renal Dialysis/	61137
2	HD.mp.	26661
3	exp Kidney Diseases/ or exp Kidney Failure, Chronic/	265127
4	exp Catheters, Indwelling/	10418
5	exp Catheterization, Central Venous/	6308
6	exp Vascular Fistula/	9039
7	exp Arteriovenous Fistula/	8071
8	vascular access.mp.	2650
9	fistula.mp.	34765
10	catheter$.tw.	94388
11	or/1-3	293156
12	or/4-10	137098
13	11 and 12	8846
14	limit 13 to human	8464
15	limit 14 to English language	6689
16	limit 15 to yr=1997-2004	2741
17	limit 16 to (addresses or bibliography or biography or case reports or congresses or consensus development conference or consensus development conference, nih or dictionary or directory or editorial or festschrift or government publications or interview or lectures or legal cases or legislation or letter or news or newspaper article or patient education handout or periodical index)	736
18	16 not 17	2005
19	limit 18 to (guideline or meta analysis or practice guideline or review or review, academic or review literature or review, multicase or review of reported cases or review, tutorial)	372
20	18 not 19	1633
21	follow-up studies/	287082
22	(follow-up or follow.up).tw.	307677
23	exp Case-Control Studies/	261329
24	(case adj20 contro$).tw.	39852
25	exp Longitudinal Studies/	488492
26	longitudinal.tw.	56837
27	exp Cohort Studies/	501708
28	cohort.tw.	51894
29	(random$ or rct).tw.	201685
30	exp Randomized Controlled Trials/	33666
31	exp random allocation/	51582
32	exp Double-Blind Method/	79233
33	exp Single-Blind Method/	8332
34	randomized controlled trial.pt.	192490
35	clinical trial.pt.	389032
36	(clin$ adj trial$).tw.	80094
37	((sing$ or doub$ or treb$ or trip$) adj (blind$ or mask$)).tw.	75835
38	exp placebos/	23205
39	placebo$.tw.	85529
40	exp Research Design/	183137
41	exp Evaluation Studies/	495446
42	exp Prospective Studies/	175699
43	exp Comparative Study/	1142862
44	or/21-43	2574058
45	20 and 44	1046
46	20 not 45	587
47	exp arteriovenous shunt, surgical/	5614
48	(Arteriovenous adj5 graft$).tw.	645

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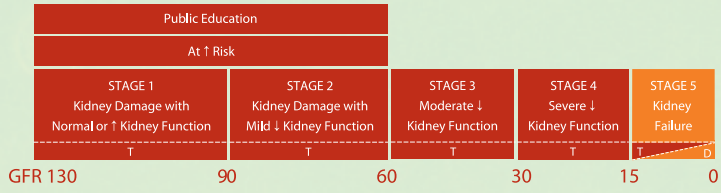

Light-shaded boxes indicate the scope of content targeted in this resource.
GFR = Glomerular Filtration Rate; T = Kidney Transplant; D = Dialysis

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