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

SECTION I: USE OF THE CLINICAL PRACTICE GUIDELINES AND CLINICAL PRACTICE RECOMMENDATIONS

These Clinical Practice Guidelines (CPGs) and Clinical Practice Recommendations (CPRs) are based upon the best information available at the time of publication. They are designed to provide information and assist decision-making. They are not intended to define a standard of care, and should not be construed as one. Neither should they be interpreted as prescribing an exclusive course of management.

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.

SECTION II: DISCLOSURE

The National Kidney Foundation makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the Work Group.

Specifically, all members of the Work Group are required to complete, sign, and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest. All affiliations are published in their entirety at the end of this publication in the Biographical Sketch section of the Work Group members.

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These guidelines as well as other KDOQI guidelines, can be accessed on the Internet at **www.kdoqi.org**.

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

Hemodialysis Adequacy Figures

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.

PERITONEAL DIALYSIS ADEQUACY

Peritoneal Dialysis Adequacy 2006

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Peritoneal Dialysis Adequacy Tables

Peritoneal Dialysis Adequacy Acronyms and Abbreviations

ACE	Angiotensin-converting enzyme
ADEMEX	Adequacy of Peritoneal Dialysis in Mexico
APD	Automated peritoneal dialysis
ARB	Angiotensin receptor blocker
AV	Arteriovenous
BMI	Body mass index
BSA	Body surface area
CANUSA	Canada-United States Study
CAPD	Continuous ambulatory peritoneal dialysis
CCPD	Continuous cycling peritoneal dialysis
C_{Cr}	Creatinine clearance
CHF	Congestive heart failure
CI	Confidence interval
CKD	Chronic kidney disease
CMS CPM	Centers for Medicare and Medicaid Services Clinical Performance Measures Project
COX-2	Cyclooxygenase-2
CPG	Clinical Practice Guideline
CPR	Clinical Practice Recommendation
CQI	Continuous quality improvement
CRP	C-Reactive protein
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
D/D_0	End dwell dialysate dextrose over initial dialysate dextrose
DOQI	Dialysis Outcomes Quality Initiative
D/P	Dialysate to plasma ratio
DPI	Dietary protein intake
DV	Drain volume of peritoneal effluent
EAPOS	European Automated Peritoneal Dialysis Outcome Study
ECF	Extracellular fluid
GFR	Glomerular filtration rate
HD	Hemodialysis
HR	Hazard ratio
IDEAL	Initiating Dialysis Early And Late
IPP	Intraperitoneal pressure
KDOQI	Kidney Disease Outcomes Quality Initiative
KLS	Kidney Learning System

KRT	Kidney replacement therapy
Kt/V_{urea}	Urea nitrogen clearance divided by volume of distribution of urea nitrogen
LBW	Low birth weight
LVH	Left ventricular hypertrophy
LVM	Left ventricular mass
LVMI	Left ventricular mass index
MAP	Mean arterial blood pressure
MDRD	Modification of Diet in Renal Disease
MTAC	Mass transfer area coefficients
NAPRTCS	North American Pediatric Renal Transplant Cooperative Study
nd	No data reported
NECOSAD	Netherlands Cooperative Study on the Adequacy of Dialysis
NIPD	Nightly intermittent peritoneal dialysis
NKF	National Kidney Foundation
nPCR	Normalized protein catabolic rate
nPNA	Normalized protein equivalent of total nitrogen appearance
NS	Not significant
NSAIDs	Nonsteroidal anti-inflammatory drugs
OR	Odds ratio
p^{C}_{Cr}	Peritoneal creatinine clearance
PCR	Protein catabolic rate
PD	Peritoneal dialysis
PDC	Peritoneal dialysis capacity test
PET	Peritoneal equilibration test
PNA	Protein equivalent of total nitrogen appearance
QOL	Quality of life
RCT	Randomized controlled trial
rGFR	Residual glomerular filtration rate
RKF	Residual kidney function
ROC	Receiver operating characteristic
RR	Relative risk
SBP	Systolic blood pressure
SD	Standard deviation
SGA	Subjective global assessment
SPA	Standard peritoneal permeability analysis
TBW	Total body water
TNa	Total sodium removal
TUF	Total ultrafiltration
UF	Peritoneal ultrafiltration
USRDS	United States Renal Data System
UV	Urine volume
V	Volume of distribution of urea nitrogen

Foreword

THE PUBLICATION of the Clinical Practice Guidelines (CPGs) and Clinical Practice Recommendations (CPRs) for Peritoneal Dialysis Adequacy 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 peritoneal dialysis patients. 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 peritoneal dialysis patients since the publication of the first set of guidelines. The Adequacy of Peritoneal Dialysis in Mexico (ADEMEX) Study, an industry-sponsored randomized clinical trial of dialysis dose, is one of the largest studies to date performed in long-term peritoneal dialysis patients. Other large clinical trials in peritoneal dialysis patients have been conducted in Hong Kong. The results of these and other studies of long-term peritoneal dialysis patients have been included in the literature review for this updated set of guidelines and are reflected in new minimum levels for the dose of dialysis. 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 Peritoneal Dialysis Adequacy has undergone extensive revision in response to comments during the public review. While 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 Burkart from Wake Forest University and Beth Piraino from The University of Pittsburgh. It is their commitment and dedication to the KDOQI process that has made this document possible.

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INTRODUCTION

This publication represents the second revision of the Kidney Disease Outcomes Quality Initiative (KDOQI) Guidelines for Peritoneal Dialysis (PD) Adequacy. The revision was precipitated in part by the publication of 2 prospective randomized trials that evaluated the relationship between small-solute clearance and short-term outcomes in patients on PD therapy. These studies represent a higher level of evidence for guideline formation than were available to formulate the first 2 Dialysis Outcome Quality Initiative (DOQI) and KDOQI Guidelines for PD Adequacy. The results of both studies suggested that improving survival on currently available PD therapies likely is related to factors other than increasing small-solute clearances. Data continued to emerge that confirmed the importance of maintaining residual kidney function (RKF) and a guideline reflecting the importance of RKF on patient outcomes was added. In addition, there were preliminary data suggesting that surrogates for cardiovascular risk (peritoneal ultrafiltration and volume removal) were predictive of relative risk (RR) for death in cohort observational studies. Although the Work Group acknowledges that these data are preliminary, we believed that recommendations for volume and blood pressure control in PD patients could now be added.

In contrast to the second version of the KDOQI Guidelines for PD Adequacy, the current guidelines represent a complete revision of the original. In addition to modifications of the actual guidelines based on new medical evidence, clinical and practical experiences with use of the original guidelines also were reviewed and, when appropriate, incorporated. Most importantly, we attempted to address issues related to experiences with implementation of the guidelines, work load on dialysis unit staff, and use of the guidelines for formulating clinical performance measurements by some oversight bodies.

These guidelines are primarily for patients on continuous ambulatory PD (CAPD) therapy. There are limited data for automated PD (APD) and no randomized controlled trials (RCTs). Therefore, we cannot formulate guidelines for APD, and any comments on this form of therapy are mainly opinion based. Further study is needed in this area.

Because children are not "small adults," guidelines for children have been separated into 1 section (Guideline 6). These mirror the adult guidelines, but follow the pediatric literature. For areas in which no pediatric-specific data exist, the adult guidelines should serve as a minimum standard for pediatric patients.

Despite voicing concerns in the original DOQI publications, at times guidelines were used by oversight bodies in a way not intended by the Work Group and—at other times—not in keeping with the spirit in which the guidelines were formulated. As a result, this publication is organized differently, into: (1) Clinical Practice Guidelines (CPGs); and (2) Clinical Practice Recommendations (CPRs). The guidelines are based on available evidence such as it exists. Much more information is needed; therefore, we would strongly discourage oversight bodies from using these CPGs for clinical performance measurements. The CPRs are based on weak evidence or opinion and as such, should not be used for clinical performance measurements. In particular, because of the absence of RCTs for patients on APD therapy, no clinical performance measurements regarding this form of therapy are appropriate. Guidelines are meant to inform, but not replace, clinical judgment.

Finally, we must express some caveats and cautions about the guidelines. In contrast to the original guidelines, in which a target total solute clearance was recommended, in the present guidelines, a minimal dose is recommended. When using a target, even if a patient was below target, solute clearance would still likely be adequate. Conversely, when using a minimal dose, there is less room for error. All patients should be above the minimal. Additionally, data from prospective randomized trials are based on relatively short-term trials of patients on PD therapy in Mexico and Hong Kong. These patients likely are on different protein intakes and perhaps are more likely to be adherent with the PD prescription than the typical patient in the United States. As a result, the current document emphasizes patient observations and adjustment of the PD prescription if the patient is not doing well clinically. There is a paucity of knowledge regarding small-molecule clearance targets and long-term complications, such as calcium-phosphate product effects and uremic neuropathy. Additional data are required to make recommendations for optimization of long-term health.

The prior publications recognized that there was an absence of RCTs to answer important questions regarding PD adequacy and optimal practice. The prior guidelines identified research needs, some of which have been met. We hope that the present guidelines identify questions that will stimulate further research, improve patient outcomes, and advance the clinical practice of PD.

I. Clinical Practice Guidelines for Peritoneal Dialysis Adequacy

GUIDELINE 1. INITIATION OF DIALYSIS

1.1 Preparation for kidney failure:
Patients who reach chronic kidney disease (CKD) stage 4 (estimated glomerular filtration rate [GFR] < 30 mL/min/1.73 m^2) should receive timely education about kidney failure and options for its treatment, including kidney transplantation, peritoneal dialysis (PD), hemodialysis (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 (KRT). 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 militate 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 by the constraints of regulation and reimbursement.

Table 1. Validated GFR-Estimating Equations

Age ≥18 Years
Cockcroft-Gault Equation[1]
MDRD 4 Variable Equation[3]
MDRD 6 Variable Equation[2]
Age <18 Years
Schwartz Formula[4]

MDRD: Modification of diet in renal disease

For some patients, conservative therapy without dialysis or transplantation is the appropriate option.[10–12] If the patient makes this choice, the health care team should strive to maximize the quality of life (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, keto-analogs of essential amino acids, loop diuretics, and sodium polystyrene sulfonate. Nephrologists also should be familiar with the principles of palliative care[13] 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.[14] 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 the scheduling of consultations, tests, and procedures. Results of access creation procedures vary, and

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

Condition	Creatinine Generation
Vegetarian diet[5]	Low
Muscle wasting[5]	Low
Amputation[5]	Low
Spinal cord injury[6]	Low
Advanced liver disease[7,8]	Low
Muscular habitus[5]	High
Asian race[9]	Low

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

Drug or Condition	Kidney Tubular Creatinine Secretion
Trimethoprim[5]	Low
Cimetidine[5]	Low
Fibrates (except gemfibrizol) [5]	Low
Advanced liver disease[5]	High

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 the 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 the 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.[15]

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, 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 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.[16–19]

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, absence of symptoms despite underlying kidney

disease, transplantation eligibility, choice between PD and HD, and 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 serum creatinine level 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.[20]

Variation in Creatinine Generation. It is well established that creatinine generation may be unusually low in patients with a number of conditions and that it 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 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 attributable directly or indirectly to loss of kidney function and initiate kidney replacement therapy (KRT) earlier in such patients. However, they should consider that dialysis is not innocuous, 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, 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 a patient's QOL by extending the dialysis-free period while avoiding complications that will reduce 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 National Kidney Foundation NKF KDOQI HD Adequacy Guideline.[21–23] 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.[24]

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.[25–28] However, others suggested that worse kidney function at initiation of KRT is associated with increased mortality or morbidity.[23,24,29] 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 a higher versus lower GFR.[30,31]

Furthermore, it now is clear from observational registry data from the United States, Canada, and the United Kingdom (www.renalreg.com/Report%202003/Cover3_Frames.htm)[31A] that patients with comorbidities initiate dialysis therapy at higher levels of estimated GFR.[24,32,33] 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 the hardy patients who start dialysis therapy 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 RCT to compare a broad range of outcomes in patients starting dialysis with a Cockcroft-Gault GFR of 10 to 14 versus 5 to 7 mL/min/1.73 m^2.[34]

In 2000, the NKF KDOQI Clinical Practice Guideline 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 therapy—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.[35] 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 to 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. PERITONEAL DIALYSIS SOLUTE CLEARANCE TARGETS AND MEASUREMENTS

Data from RCTs suggested that the minimally acceptable small-solute clearance for PD is less than the prior recommended level of a weekly Kt/V_{urea} of 2.0. Furthermore, increasing evidence indicates the importance of RKF as opposed to peritoneal small-solute clearance with respect to predicting patient survival. Therefore, prior targets have been revised as indicated next.

2.1 For patients with RKF (considered to be significant when urine volume is > 100 mL/d):

2.1.1 The minimal "delivered" dose of total small-solute clearance should be a total (peritoneal and kidney) Kt/V_{urea} of at least 1.7 per week. (B)

2.1.2 Total solute clearance (residual kidney and peritoneal, in terms of Kt/V_{urea}) should be measured within the first month after initiating dialysis therapy and at least once every 4 months thereafter. (B)

2.1.3 If the patient has greater than 100 mL/d of residual kidney volume and residual kidney clearance is being considered as part of the patient's total weekly solute clearance goal, a 24-hour urine collection for urine volume and solute clearance determinations should be obtained at a minimum of every 2 months. (B)

2.2 For patients without RKF (considered insignificant when urine volume is ≤100 mL/d):

2.2.1 The minimal "delivered" dose of total small-solute clearance should be a peritoneal Kt/V_{urea} of at least 1.7 per week measured within the first month after starting dialysis therapy and at least once every 4 months thereafter. (B)

BACKGROUND

Previous studies suggested that improved survival on PD therapy was associated with higher total small-molecule clearances.[36] Extrapolations from the Canada-United States (CANUSA) Study led to the prior guidelines of a total weekly Kt/V_{urea} of 2.0 and creatinine clearance (C_{Cr}) of 60 L/wk/1.73 m^2 for CAPD patients. Higher targets were chosen for continuous cycling PD (CCPD) and patients on APD with no daytime dwell (dry day), and, in the absence of data, based on theoretical considerations. Reanalysis of the CANUSA Study showed that RKF, rather than peritoneal clearance, was associated with improved survival.[37] Greater urine volume was a significant and important predictor of better survival, as well. Results of this reanalysis subsequently were supported by the Adequacy of PD in Mexico (ADEMEX) Study randomized trial of CAPD patients comparing 2 levels of PD prescription.[38] The 2 groups of patients had identical survival, indicating no benefit on survival for greater small-molecule peritoneal clearance and confirming the benefit of RKF on survival. Further support was supplied by another randomized trial of CAPD patients from Hong Kong[39] comparing 3 levels of total

Kt/V_{urea} in patients with small degrees of RKF, with the lowest group randomized to a total Kt/V_{urea} of 1.5 to 1.7, with no difference in survival. Therefore, revision of the previous guidelines is needed.

RATIONALE

Definitions

Total small-molecule clearance should be measured as Kt/V_{urea} and is based on a 24-hour collection of urine (kidney Kt/V_{urea}; if volume >100 mL/d) and a 24-hour collection of effluent for CAPD and APD, a sample of the effluent, and the total drained effluent volume (peritoneal Kt/V_{urea}; adding ultrafiltration with the infused dialysate volume). The term RKF is used to refer to estimated GFR, measured as the average of C_{Cr} and urea nitrogen clearance based on a 24-hour urine collection. Urine volume in 24 hours of 100 mL or less is considered to represent negligible RKF, although there are few data to indicate at what level kidney function becomes "negligible." The term "delivered" peritoneal Kt/V_{urea} refers to the actual dose the patient is receiving based on measurement using the described method. This is distinct from an estimated peritoneal Kt/V_{urea} using a kinetic modeling program. "Delivered" Kt/V_{urea} assumes that the collection on the day the clearance is measured is representative of the patient's typical dialysis schedule and that the patient follows this same prescription every day.

For patients with RKF (considered to be significant when urine volume is >100 mL/d): the minimal "delivered" dose of total small-solute clearance should be a total (peritoneal and kidney) Kt/V_{urea} of at least 1.7 per week. (moderately strong evidence). Table 4 summarizes the effect of clearance on patient survival. In the ADEMEX Study, CAPD patients were randomized to continue on 4 exchanges using 2 L per exchange or to an increase in the prescription to provide a peritoneal clearance of 60 L/wk/1.73 m^2 by either an increase in exchange volume or the addition of a nighttime exchange or both.[38] The 2 groups had identical overall survival. Those with a mean total weekly Kt/V_{urea} of 2.27 had patient and technique survival equivalent to that of patients with a mean total Kt/V_{urea} of 1.80.[38] Peritoneal small-molecule clearances bore no relationship to survival. In this study, body mass indices (BMIs) in the 2 groups were 25.3 and 25.8 kg/m^2, and 42% to 45% of patients had diabetes, respectively. Patients were followed up for a minimum of 2 years, with 2-year survival rates of 68.3% and 69.3%, respectively. Approximately one half the patients had some RKF. The number of deaths in the 2 groups was identical, although causes of death varied slightly. In the ADEMEX Study, the group randomized to the lower prescription had slightly, but significantly, more deaths from congestive heart failure (CHF) and more deaths ascribed to uremia and hyperkalemia. This was balanced by an insignificantly higher number of deaths in the intervention group caused by coronary artery disease and peritonitis (although peritonitis rates were not higher). Deaths caused by CHF may have been greater in the control arm because ultrafiltration was less in this group (130 mL/d less, which represents 3.9 L/mo), likely because patients randomized to the higher prescription achieved this level through increased exchange volume (which is associated with higher ultrafiltration volumes) and,

Table 4. Effect of Clearance on Patient Survival

Author, Year	Study Design	Frequency of Measurement	N	Follow-up (Maximum)	Applicability	Predictor	Results (95% CI) P value			Quality
							RKF	Peritoneal Clearance	Total Kt/V_{urea}	
Pariagua, 2002[38]	RCT	Every 4 mo	965	22 mo	↑↑↑	Kt/V_{urea}: ↑ 0.1 mL/min	RR = 0.94 P = 0.005	RR = 1.0 NS		●
Lo, 2003[39]	RCT	6 mo	320	24 mo	↑↑↑	Kt/V_{urea} ↑ 0.1 mL/min			RR = 0.94 (0.88, 1.02) NS	●
Rocco, 2000[79]	Prospective	Average (if more than 1 measurement)	1446	(7 mo)	↑↑↑	Kt/V_{urea}: 0.1 U/wk	OR = 0.88 (0.81, 0.96) P = 0.003	OR = 1.0 (0.9, 1.1) NS	OR = 0.6 (0.4, 1.1) P = 0.08	○
Bargman, 2001[37]	Prospective	Baseline and 6 mo interval	601	(24 mo)	↑↑↑	rGFR: ↑ 5 L/wk/1.73 m²	RR = 0.88 (0.83, 0.94) P <0.05			○
						pC_{Cr}: ↑ 5 L/wk/1.73 m²		RR = 1.00 (0.90, 1.11) NS		
Termorshuizen, 2003[44]	Prospective	After 3 mo, then at 6 mo intervals	413	(36 mo)	↑↑↑	rGFR mL/min/1.73 m²	RR = 0.88 (0.79, 0.99) P = 0.04			○
						pC_{Cr} mL/min/1.73 m²		RR = 0.91 (0.71, 1.17) NS		
Davies, 1998[81]	Prospective longitudinal	Baseline and 6 mo interval	210	6 mo	↑↑↑	Kt/V_{urea} per U/wk			RR = 0.17 P = 0.004	○
Jager, 1999[46]	Prospective multicenter	3 mo after initiation	118	25 mo	↑↑↑	Kt/V_{urea}: 0.1 U/wk	RR = 0.96[a] (0.88, 1.05) NS	RR = 0.95[a] (0.84, 1.08) NS	RR = 0.93[a] (0.85, 1.02) NS	○
Lo, 2001[80]	Prospective	nd	937	24 mo	↑↑	rGFR: ↑ 1 mL/min/1.73 m²	RR = 0.87[a] (0.72, 1.06) NS			○
						C_{Cr}: ↑ 1 L/wk		RR = 0.99[a] (0.98, 1.01) NS		
Szeto, 2004[58]	Prospective	At least yearly	270	35 mo	↑↑	Kt/V_{urea}: ↑ 0.1 mL/min		RR = 0.94 (0.89, 0.99) P = 0.03		○
						rGFR: ↑ 1 mL/min/1.73 m²	RR = 0.80 (0.73, 0.88) P = 0.000			

(Table continued on page 136 & 137)

Table 4. Effect of Clearance on Patient Survival (cont.)

Author, Year	Study Design	Frequency of Measurement	N	Follow-up (Maximum)	Applicability	Predictor	Results (95% CI) P value			Quality
							RKF	Peritoneal Clearance	Total Kt/V_{urea}	
Szeto, 2000[41]	Prospective	At least yearly	270	22 mo	↑↑	Kt/V_{urea}: ↑ 0.1 mL/min			RR = 0.95 (0.93, 0.99) P <0.05	●
						rGFR: ↑ 1 mL/min/1.73 m²	RR = 0.48 (0.02, 0.93) P <0.05			
Szeto, 2001[67]	Prospective	At least yearly	140 (anuric)	22 mo	↑↑	Kt/V_{urea}: ↑ 0.1 mL/min		RR = 0.94 (0.92, 0.99) P <0.05		●
Chung, 2003[45]	Prospective	nd	82	14 mo	↑↑	Kt/V_{urea}: ↑ 0.1 mL/min			RR = 1.09 (0.96, 1.24) NS	●
						rGFR*: ↑ 1 mL/min/1.73 m²	RR = 0.79 (0.55, 1.08) NS			
Wang, 2004[43]	Prospective	nd	231	30 mo	↑↑	RKF vs. no RKF	No RKF: higher mortality P <0.005*			○
Perez, 2000[62]	Prospective	At start and 3 mo	44	13 mo	↑	Kt/V_{urea}: ↑ 0.1 mL/min			RR = 1.02 NS	○
Diaz-Buxo, 1999[42]	Retrospective cohort	nd	2686	(1 yr)	↑↑↑	C_{Cr}: ↑ 10 L/wk	OR = 0.88 P <0.001	OR = 1.01 NS	OR = 0.89 NS	○
Rocco, 2002[40]	Retrospective cohort	Every 2 mo	1,219	(1 yr)	↑↑↑	Kt/V_{urea} 0.00-0.14	HR = 2.13 (1.24, 3.68) P<0.01			○
						0.15-0.40	HR = 1.67 (0.87, 3.20) NS			
						0.41-0.77	HR = 1.35 (0.70, 2.62) NS			
						>0.77	Reference			
Park, 2001[33]	Retrospective cohort	Within 3 mo	212	nd	↑↑↑	Kt/V_{urea}/wk<2.1 vs. >2.1			NS*	○
Chung, 2003[45]	Retrospective cohort	nd	117	20 mo	↑↑↑	RKF per 1 mL/min	RR = 0.79 (0.62, 0.99) P = 0.04			○
Ates, 2001[48]	Retrospective cohort	Every 2 mo	125	31 mo	↑↑	rGFR: ↑ 1 mL/min/1.73 m²	RR = 0.53 (0.31, 0.91) P <0.05			●

(Table continued on page 137)

Table 4. Effect of Clearance on Patient Survival (cont.)

Author, Year	Study Design	Frequency of Measurement	N	Follow-up (Maximum)	Applicability	Predictor	Results (95% CI) P value			Quality
							RKF	Peritoneal Clearance	Total Kt/V_{urea}	
Bhaskaran, 2000[73]	Retrospective cohort	Every 3 mo	122 (anuric)	27 mo	↑↑	pKt/V ≥1.85 vs. pKt/V <1.85		RR = 0.54 (0.26, 1.13) NS		○
Aslam, 2000[84]	Retrospective cohort	Every 4-6 mo	90	(1 yr)	↑↑	Kt/V_{urea} ≥2 vs. Kt/V_{urea} <2			86.3% vs. 80.9% NS[a]	○

a. Univariate analysis
b. rGFR was calculated as the mean of renal creatinine and urea clearance adjusted for body surface area.
nd – no data

if necessary, a fifth exchange using a nighttime exchange device. Therefore, this difference in mortality caused by CHF may be due to differences in fluid removal.

QOL also was assessed in the ADEMEX Study. There were no significant differences between the 2 groups at any time for physical composite summary score, mental composite summary score, or kidney disease component summary.[40] Therefore, neither survival nor QOL was benefited by greater small-molecule clearances.

Results of the ADEMEX Study are consistent with a subsequent randomized trial in Hong Kong comparing total Kt/V_{urea} values of 1.5 to 1.7, 1.7 to 2.0, and greater than 2.0 in CAPD patients.[39] There were no differences in patient survival in the 3 groups. All patients at the start of the study had residual kidney Kt/V_{urea} of 1.0 or less, ensuring minimal RKF. Baseline residual GFRs (rGFRs) were 2.38, 2.48, and 2.64 mL/min/1.73 m^2, respectively (representing kidney Kt/V_{urea}s of 0.44, 0.46, and 0.49 in the 3 groups, respectively; not a significant difference). Average BMI was 22 kg/m^2, somewhat smaller than that of patients in the ADEMEX Study. The usual prescription was three 2-L exchanges per day, as opposed to four 2-L exchanges in the control arm of the ADEMEX Study. During the course of the 2-year study, PD prescription was adjusted up or down as RKF changed to stay within the randomized total Kt/V_{urea} category. By the end of the study, residual kidney Kt/V_{urea} was at or less than 0.1 in all 3 categories. Dialysis adequacy was assessed every 6 months. Results of these 2 important studies highlight the need to look at factors other than small-molecule clearance to improve survival in PD patients because peritoneal small-molecule clearance was not a predictor of survival, hospitalization, or nutritional state.

Observational studies support the findings of these 2 randomized trials, indicating that RKF (in those with RKF), rather than level of peritoneal small-molecule clearance, predicts survival, as well as QOL.[41] In a large group of US PD patients (1,603 patients), age and serum albumin level were predictors of death, as was RKF; however, peritoneal clearance was not.[42] Another study of 763 patients found that neither peritoneal Kt/V_{urea} nor peritoneal C_{Cr} was predictive of 1-year mortality.[43] This population consisted of 53% CAPD and 34% CCPD patients; the rest were on both modalities during the 6-month study period or information was missing. In a longitudinal study of 412 adult PD patients (mean age, 52 years; 66.3% men, 15.3% with diabetic nephropathy), survival was predicted by GFR (RR, 0.88; 95% confidence interval [CI], 0.79 to 0.99; $P = 0.039$) and not peritoneal C_{Cr}. Comorbidity, albumin level at baseline, and age also were predictive of survival. Transport status was not a predictor of survival in this cohort. Kidney rGFR also was associated with multiple measures of better QOL, in contrast to peritoneal clearance, which was not associated with any component of QOL.[44] In yet another study,[45] transport status was not associated with survival, but survivors had significantly more residual function than those who did not survive (4.5 versus 2.8 mL/min/1.73 m^2). Low initial RKF was associated with greater C-reactive protein (CRP) levels, indicating a relationship between inflammation and loss of RKF.

Observational studies suggest that volume status is closely linked to PD patient survival, as shown in Table 5. In a study from The Netherlands of 118 consecutive new PD patients examined in a prospective observational multicenter cohort study using Cox

Table 5. Effect of Fluid Removal on Clinical Outcomes

Author, Year	Study Design	N	Follow-up (Maximum)	Applicability	Predictor	Outcome	Results (95% CI) P value		Quality
							Multivariate	Univariate	
Mortality									
Jager, 1999[46]	Prospective	118	25 mo	↑↑↑	UF: per 500 mL/24 hr increase	Mortality		RR = 1.05 (0.86, 1.27) NS	○
					TUF[a]: per 500 mL/24 hr increase			RR = 1.02 (0.85, 1.22) NS	
Bargman, 2001[37]	Prospective	680	(24 mo)	↑↑	UV: per 250 mL/24 hr increase	Mortality	RR = 0.64 (0.51, 0.80) P <0.05		○
Brown, 2003[71]	Prospective	177	(2 yr)	↑↑	TUF: per 1000 mL/24 hr increase	Mortality	RR = 0.45 P = 0.047		○
Ates, 2001[48]	Retrospective cohort	125	31 mo	↑↑	Total fluid removal: per 100 mL/24 hr/1.73 m² increase	Mortality	RR = 0.90 (0.84-0.96) P <0.01	RR = 0.88 (0.83, 0.95) P <0.01	○
					TNa: per 10 mmol/24 hr/1.73 m² increase		RR = 0.90 (0.84-0.96 P <0.001	RR = 0.86 (0.80, 0.92) P <0.0001	
Blood Pressure									
Jager, 1999[46]	Prospective	118	25 mo	↑↑↑	SBP 10 mm Hg increase	Mortality	RR = 1.42 (1.17-1.73) P <0.001		○
Tonbul, 2003[85]	Prospective	25	(1 mo)	↑↑	TUF[a]: 1086 vs. 1493 mL/24 hr	SBP		145 vs. 128 P <0.001	○
						DBP		97 vs. 81 P <0.001	
Woodrow, 2000[81]	Prospective	14	(1 mo)	↑	UF: 1560 (7.5% icodextrin) vs. 1410 (2.27% glucose) mL/24 hr	SBP		142 vs. 123 P <0.005	○
						DBP		83 vs. 77 P = 0.08	
Ates, 2001[48]	Retrospective cohort	125	31 mo	↑↑	Hypertension present	Mortality	RR = 5.61 (1.97-15.93) P = 0.001		○

a. TUF = urine volume + ultrafiltration
b. Study comparing blood pressure change before and after increase in ultrafiltration.

proportional hazards regression, systolic blood pressure (SBP; RR, 1.42 for every 10 mm Hg increase in blood pressure) was a predictor of survival, but peritoneal Kt/V_{urea} was not a predictor of survival, nor was kidney rGFR.[46] Another study from The Netherlands examined poor outcomes (death or at least 2 of the following: prolonged hospitalization, serum albumin ≤3 g/dL, or malnutrition) in 189 patients and found that a model including comorbidity, serum albumin level, and physical and mental QOL was predictive of poor outcome, with a receiver operating characteristic (ROC) value of 0.84. A post hoc analysis excluding serum albumin level and QOL found that mean arterial blood pressure (MAP) was a strong predictor of poor outcome (MAP >107 mm Hg had an 8.6 times greater risk compared with MAP <107 mm Hg; $P = 0.005$), but only in PD patients, not HD patients.[47] Similar results were found in an observational study from Turkey examining outcomes in 125 PD patients (who had survived ≥6 months on PD therapy), 92% of whom were on CAPD therapy. Comorbidity, serum creatinine level (likely a measure of nutrition), RKF, and hypertension (RR, 5.6; $P = 0.001$), but not peritoneal clearance, were predictors of survival.[48] Another study showed that CRP level, RKF, and left ventricular mass index (LVMI) were all predictive of both all-cause mortality and cardiovascular death.[49] An analysis of United States Renal Data System (USRDS) Wave 2 data regarding blood pressure in PD patients found that only low blood pressure (<111 mm Hg) was predictive of death, clearly a reflection of poor cardiac function because the finding was only present in those with a prior history of CHF (positive or suspected, 68% of total group).[50] Of those with low blood pressure—in patients not administered antihypertensive medications (18% of total)—there were no associations between blood pressure and mortality. It is unclear whether this negative effect of low blood pressure was caused by a harmful effect on RKF, but this seems possible. All these studies suggest that close attention to volume status and blood pressure control are important in maximizing PD patients' chances of survival. Because of the emerging evidence about the importance of euvolemia, the Work Group has added Guideline 4.

Serum albumin level has been shown repeatedly to be a predictor of survival in dialysis patients. In a retrospective study from Turkey of 334 patients on CAPD therapy, survival was predicted by age, serum albumin level, cormorbid conditions (including peripheral vascular disease), and functional status, but not by Kt/V_{urea}.[51] There are many causes of low albumin levels, including poor intake, chronic inflammation, chronic liver disease, volume overload, metabolic acidosis, and inadequate dialysis.[52] There is little evidence that increasing small-molecule clearance improves serum albumin level. In neither the ADEMEX Study nor the randomized study from Hong Kong did higher peritoneal clearances lead to improvement in nutritional status.

Other maneuvers appear to be more successful in improving nutritional status. In a blinded randomized placebo-controlled trial of 60 CAPD patients with a total Kt/V_{urea} of 1.91 to 1.93 at the start of the study (and RKF of 1.78 to 1.91 mL/min), oral bicarbonate replacement was associated with an improvement in subjective global assessment (SGA) score and a decrease in anorexia.[53] By the end of this 52-week study, total average Kt/V_{urea} values were 1.77 (treatment) and 1.78 (placebo). Three randomized trials examined the use of supplements to improve protein malnutrition.[54–56] Protein powder (15

g [equivalent to 11 g of high biological value protein] administered twice daily) in CAPD patients with a total average Kt/V_{urea} of 1.7 to 1.8 was effective in improving SGA scores,[55] whereas an oral liquid protein supplement was not effective, in large part because of poor tolerance.[56] Likewise, a randomized trial of amino acid tablets in PD and HD patients found that the supplement improved serum albumin levels in HD patients, but not PD patients; adherence was poor in PD patients.[54]

Overhydration also is a cause of hypoalbuminemia in PD patients.[57] Twenty-one patients (15 patients, CAPD; 6 patients, CCPD) had an increase in serum albumin level, decrease in blood pressure, and decrease in number of antihypertensive drugs after adjustment of the PD prescription to increase fluid removal. Therefore, the existing evidence suggests that if Kt/V_{urea} is 1.8 or greater and serum albumin level is low, attention should be directed toward correcting metabolic acidosis and fluid overload and consideration should be given to a palatable protein supplement. If Kt/V_{urea} is borderline (ie, <1.8), consideration should be given to increasing the dose of PD and to assessment of adherence with the prescription.

Surprisingly few data are available regarding the relationship between peritoneal small-molecule clearance and technique survival (Table 6). In the ADEMEX Study, overall withdrawal from the study and technique survival were similar for the 2 groups on differing PD prescriptions.[38] Cause of withdrawal varied, with more patients in the control group withdrawing because of uremia (compared with none in the intervention group); however, by virtue of the study design, neither patients nor physicians could be blinded to the group. In the randomized trial from Hong Kong,[39] withdrawal from the study was 6% because of inadequate dialysis and 8% because of inadequate ultrafiltration for the group randomized to a total Kt/V_{urea} of 1.5 to 1.7 compared with no patients withdrawn because of inadequate dialysis in the group randomized to a total Kt/V_{urea} of 1.7 or greater. In an observational study, higher peritoneal Kt/V_{urea} was an independent predictor of better technique survival in a group of patients with an average peritoneal Kt/V_{urea} of 1.59.[58] In another observational study from the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD)[44] combining patient and technique survival, there was no effect of peritoneal clearance on outcome. In 413 patients at 3 months on dialysis therapy, renal weekly Kt/V_{urea} was 0.82 and peritoneal weekly Kt/V_{urea} was 1.52. At 36 months of follow-up, 31 patients remained in the cohort, with essentially the same renal and peritoneal Kt/V_{urea} values. These results taken together suggest that setting the minimal total Kt/V_{urea} target at 1.7 should not have a negative impact on technique survival.

Measured total Kt/V_{urea} is not always the consistently delivered Kt/V_{urea}. Ultrafiltration may vary considerably from day to day, urine volume and GFR may fluctuate with volume status, and the patient may change the timing of the dialysis schedule or miss exchanges.[59,60] Nonadherence with PD appears to vary by race (patients of Asian extraction are very adherent, for example), age (younger patients are more nonadherent than older), employment status (employed patients are more nonadherent than unemployed), and, possibly, country, indicating cultural influences.[61,62] Therefore, in a patient who is not doing well on PD therapy, assessment of performance of the PD should be done.

Table 6. Effect of Clearance on Technique Survival

Author, Year	Study Design	Frequency of Measurement	N	Follow-up (Maximum)	Applicability	Predictor	Results (95% CI) P value			Quality
							RKF	Peritoneal Clearance	Total Kt/V_{urea}	
Szeto, 2000[51]	Prospective	At least yearly	270	22 mo	↑↑	Kt/V_{urea}: per 0.1 U/wk increase			RR = 0.95 (0.90, 0.99) P <0.05	⊙
Szeto, [a] 2004[38]				35 mo		Kt/V_{urea}: per 0.1 U/wk increase		RR = 0.94 (0.89, 0.99) P = 0.03		
						Residual GFR: per 1 mL/min/1.73 m² increase	RR = 0.80 (0.73, 0.88) P = 0.0001			
Szeto, 2001[67]	Prospective	At least yearly	140 (anuric)	22 mo	↑↑	Kt/V_{urea}: per 0.1 U/wk increase		RR = 0.94 (0.92, 0.99) P <0.05		⊙
Perez, 2000[82]	Prospective	Start and 1-7 mo later	44	13 mo	↑	Kt/V_{urea}: per 0.1 U/wk increase			HR = 0.95	○
Bhaskaran, 2000[73]	Retrospective cohort	Every 3 mo	122 (anuric)	26 mo	↑↑	$Kt/V_{urea} \geq 1.85$ vs. $Kt/V_{urea} < 1.85$		NS		○
Aslam, 2000[84]	Retrospective cohort	Every 4-6 mo	90	(1 yr)	↑↑	$Kt/V_{urea} \geq 2$ vs. $Kt/V_{urea} < 2$			NS	○

a. A 5-year follow-up of Szeto 2000.

Adherence can be evaluated by talking to patients and assessing inventory and use of supplies.[63] In the ADEMEX Study, adherence was assessed by consumption of dialysis solutions; in the control group, 15.1 exchanges were missed per patient compared with 18.6 exchanges missed per patient in the intervention group.[38] Because follow-up was a minimum of 2 years, this indicates that less than 1 exchange was missed per month, representing excellent adherence in these Mexican patients. Adherence has not been reported in the studies from Hong Kong, but it is possible that adherence with PD exchanges is significantly and importantly better than in the United States.

Close attention must be paid to the patient's commitment to fulfilling the prescription with the new lower targets. Perceived decreased control over future health, depression, and concern over restrictions that kidney disease imposes on daily life were all predictors of nonadherence.[64] Few interventions have been done to decrease nonadherence; this is a critical area for future research.

To summarize, since the last guidelines were published, 2 randomized trials examining different levels of small-molecule clearance have been done in CAPD patients, showing no benefit of the higher small-molecule clearances on patient survival, nutritional status, hospitalization, or QOL. Emerging data suggest that the focus to improve survival in PD patients should be on preserving RKF, controlling volume overload (and thus blood pressure), treating metabolic acidosis, and perhaps use of protein supplements. Therefore, the minimal target is changed to a minimum Kt/V_{urea} of 1.7 per week, but careful attention must be paid to adherence to the prescription. The Work Group wishes to emphasize that this minimal target should not be interpreted as an average value for a program, but that each patient should have a total Kt/V_{urea} at 1.7 or higher.

For patients with RKF, total solute clearance (residual kidney and peritoneal, in terms of weekly Kt/V_{urea}) should be measured within the first month after initiating dialysis therapy and at least once every 4 months thereafter. If the patient has greater than 100 mL/d of residual kidney volume and residual kidney clearance is being considered as part of the patient's total weekly solute clearance goal, a 24-hour urine collection for urine volume and solute clearance determinations should be obtained at a minimum of every 2 months. In the CANUSA Study, RKF and peritoneal clearances were measured at baseline and every 6 months.[65] During this 2-year study, kidney C_{Cr} decreased from 38.8 to 14.3 L/wk/1.73 m^2, a rate of decrease of 1 L/wk/1.73 m^2/mo, or 0.1 mL/min/mo. The change in total small-molecule clearance was caused almost entirely by the gradual decrease in RKF because few changes were made in PD prescription. Therefore, if small-molecule clearance is dependent on RKF and the PD prescription, close monitoring of kidney function appears warranted.

In the randomized trial from Hong Kong, patients within each category had the prescription adjusted (either an increase or decrease) so that total Kt/V_{urea} was within the target of each group (1.5 to 1.7, 1.7 to 2.0, and >2.0).[39] Entry criteria required an initial kidney Kt/V_{urea} less than 1.0; average kidney Kt/V_{urea} values at the start were 0.44, 0.46, and 0.49 (not significantly different) for the 3 groups, and this number was added to the

peritoneal clearance. The PD prescription was, in turn, adjusted to reach the total target. The first adequacy assessment was done at 4 to 8 weeks after starting CAPD therapy, and a reassessment was done 4 to 6 weeks after adjusting the prescription. From that point on, clearances were obtained every 6 months. During the course of the study, there was a steady decrease in RKF in all 3 groups, such that by 37 months, average kidney Kt/V_{urea} was less than 0.1 in all 3 groups.

There is considerable variability in the rate of RKF loss in PD patients.[66] Therefore, to prevent patients from falling below the minimum total Kt/V_{urea} target of 1.7, when RKF is included in the determination, it appears prudent to obtain a 24-hour urine measurement every 2 months. Because peritoneal Kt/V_{urea} does not change much over time unless the prescription changes, every 4 months is believed to be adequate for measurement of peritoneal Kt/V_{urea} unless a change in RKF is noted.

For patients without RKF (considered to be insignificant for urine volume ≤100 mL/d), the minimal "delivered" dose of total small-solute clearance should be a peritoneal Kt/V_{urea} of at least 1.7 per week measured within the first month after starting dialysis therapy and at least once every 4 months thereafter. There are no RCTs of small-molecule clearance doses that examine outcome in only anuric patients. However, in the ADEMEX Study, anuric patients (defined as GFR <1 mL/min and constituting 56% of the control group and 54% of the intervention group) were analyzed separately. There was no survival benefit to increased small-molecule clearance in anuric patients. Although values for peritoneal Kt/V_{urea} are not given for this subset, for all patients in the study, peritoneal Kt/V_{urea} values were 1.58 and 1.59 at baseline and 1.62 and 2.13 averaged across the study duration, respectively.[38] The control CAPD prescription was 2 L times 4 exchanges. These results suggest that peritoneal Kt/V_{urea} of 1.62 in anuric CAPD patients results in the same survival as for those with Kt/V_{urea} of 2.1.

Most studies examining the relationship of Kt/V_{urea} to outcome in anuric PD patients come from Hong Kong. A descriptive study of a cohort of 140 anuric Chinese CAPD patients showed a relationship between small-molecule clearance and patient survival.[67] In this study, mean weekly Kt/V_{urea} was 1.72 (confidence limits, 1.1 to 2.23, indicating that a number of patients had low peritoneal Kt/V_{urea}). The 2-year survival rate was 68.8%, similar to the ADEMEX Study. Peritoneal Kt/V_{urea} was an independent predictor of survival at this lower range of Kt/V_{urea}.[67] The usual prescription in these smaller patients (BMI, 23.4 kg/m^2 on average) was 3 times 2 L/d, with increased volume per exchange prescribed only with poor ultrafiltration despite use of increased dextrose dialysate.

Another retrospective analysis of Chinese CAPD patients (n = 168) compared 49 anuric patients (GFR, 0.7 and 0.05 mL/min/1.73 m^2) with an average Kt/V_{urea} of 1.93 ± 0.19 with 71 patients with Kt/V_{urea} of 1.38 ± 0.22 and found that 1-year survival rates were 91.8% and 87.3%; hospitalization and technique survival were not different, but normalized protein equivalent of total nitrogen appearance (nPNA) decreased a bit more in the group with the lower Kt/V_{urea}, although this difference was insignificant (delta, 0.02 versus 0.04 g/kg/d

decrease). Of note, patients with the higher Kt/V_{urea} were on an average exchange volume of 8 L/d, whereas those with the lower clearance were on 6 L/d.[68] Anuric CAPD patients not only have greater overall mortality than nonanuric patients, the cause of the increase can be attributed to sudden cardiac death.[69] These data suggest that Kt/V_{urea} of 1.7 (>1 SD greater than the mean for the group with the lower Kt/V_{urea}) should be sufficient in anuric patients. Close attention must be paid to cardiac risk factors to prevent sudden death in these patients.

Another observational study from Hong Kong suggests some benefit of increasing dose of dialysis, but with a plateau effect. The study examined outcome and risk factors for death in 150 anuric PD patients (defined as 24-hour urine <100 mL).[70] After anuria developed (at a mean time on PD therapy of 44.1 months, with subsequent follow-up with anuria of 50.0 months), patients with a baseline peritoneal Kt/V_{urea} less than 1.67 were more likely to die than those with peritoneal clearance greater than this (RR, 1.985; $P = 0.01$). Baseline Kt/V_{urea} at the start of anuria was not predictive of mortality with Cox proportional hazard survival analysis (RR, 0.919 for every 0.1 increase, 0.833 to 1.014; $P = 0.094$). Survival was identical for those with Kt/V_{urea} greater than or less than 1.80 ($P = 0.98$), but in the subpopulation with Kt/V_{urea} less than 1.8 at baseline anuria, a subsequent Kt/V_{urea} greater than 1.76 resulted in better survival than for those with a clearance less than this ($P = 0.033$). In this observational study, PD prescription was changed to increase Kt/V_{urea} after anuria occurred. Women, in particular, were at increased risk for death with a Kt/V_{urea} less than 1.67.

An observational study compared CAPD patients with total Kt/V_{urea} of 2.03 because of significant RKF with those with total Kt/V_{urea} of 1.93 and very little RKF (RKF = 0.30 mL/min/1.73 m^2) with a third group with very little RKF and total Kt/V_{urea} of 1.38 (RKF = 0.29 mL/min/1.73 m^2).[68] Patients in the 2 groups with equivalent Kt/V_{urea} (66% and 96% because of peritoneal rather than RKF, respectively) had equivalent survival and nutritional status. The group with the lower Kt/V_{urea} (1.38; 96% from peritoneal and virtually no RKF) had equivalent survival, hospitalization, and technique survival, but baseline normalized protein catabolic rate (nPCR; grams per kilogram per day) and percentage of lean body mass were worse for those patients compared with both other groups.

A single dialysis center observational cohort study of 270 CAPD patients followed up to 6 years with average total Kt/V_{urea} of 1.78 ± 0.4 and peritoneal Kt/V_{urea} of 1.59 ± 0.37 (0.82 to 2.33) showed in prevalent patients only (as opposed to incident) that an increase of 0.1 in peritoneal Kt/V_{urea} was associated with 9% better survival (RR, 0.91; 0.85 to 0.98). Because prevalent patients would have much lower (if any) RKF, this study supports the hypothesis that only at low levels of small-molecule clearance does peritoneal clearance have an impact on survival.[58]

The European Automated Peritoneal Dialysis Outcome Study (EAPOS) was a prospective multicenter study of outcomes in anuric APD patients (n = 177).[71] One half the patients were using icodextrin for the long exchange. Time-averaged analyses showed that age, SGA grade C, and diabetic status predicted patient survival. Time-averaged C_{Cr} and baseline solute transport status had no effect on patient or technique survival. The range of C_{Cr} (liters per week per 1.73 m^2) was 55.2 to 76.6 in this study.[71] At baseline, 12% of

patients had a body surface area (BSA) greater than 2.0 m^2, and mean C_{Cr} ranged from 46 L/wk/1.73 m^2 for low-average transporters to 75 L/wk/1.73 m^2 for high transporters. EAPOS results suggest that large anuric patients, including those with low-average transport status, can be maintained successfully on APD therapy.

The NECOSAD Study Group, a prospective multicenter cohort study of new adult dialysis patients, recently released results of a study examining the relationship between small-solute clearances in anuric PD patients (n = 130).[72] At the point of anuria, patients had been on PD therapy (primarily CAPD) for an average of 13 months and peritoneal weekly Kt/V_{urea} was 1.8. Mean BMI was 24.8 kg/m^2. Anuria in this study was defined as urine output less than 200 mL/d. When Kt/V_{urea} was analyzed as a time-dependent continuous variable correcting for age, Davies score, SGA, time on dialysis therapy, serum albumin level, and hemoglobin concentration, there was no relationship with survival. When Kt/V_{urea} was analyzed as a dichotomous value (<1.7 versus ≥ 1.7), there was no relationship with survival. Only when Kt/V_{urea} was analyzed as a dichotomous value (<1.5 versus ≥ 1.5) could a relationship with survival be seen (RR, 3.28; 95% CI, 1.25 to 8.60; $P = 0.02$). These results are consistent with those of the 2 RCTs previously discussed, which did not show a survival benefit of increased small-molecule clearance in PD patients.

To summarize, although data are limited, peritoneal weekly Kt/V_{urea} of 1.7 in anuric patients on CAPD therapy appears to be an adequate minimal target. Randomized trials assessing different levels of peritoneal Kt/V_{urea} in anuric patients are needed. Randomized trials to assess different targets in APD patients also are needed.

In patients who are anuric, the dose of total small-solute clearance should be measured within the first month after starting dialysis therapy and at least once every 4 months thereafter. A retrospective analysis examined clearances in 115 anuric patients (89 patients, CAPD; 26 patients, APD).[73] Anuria was defined as urine output less than 100 mL/d or kidney C_{Cr} less than 1 mL/min. Clearance studies were obtained every 3 months. This permitted adjustment in the prescription in an attempt to meet KDOQI targets, which were Kt/V_{urea} of 2 or greater for CAPD patients and 2.2 or greater for APD patients. Fifty-six percent of patients had a change in prescription after the onset of anuria, and 25% of these patients had an additional change based on the collections. Therefore, frequent measurement of peritoneal Kt/V_{urea} in anuric patients permits timely adjustment of the prescription.

A study assigned 100 anuric CAPD patients in nonrandom fashion to either an increase (n = 50) or no change in prescription (n = 50) and repeated the clearance at 6 months.[74] Patients with an increase in prescription (peritoneal Kt/V_{urea} increased from 1.58 to 1.91) had an improvement in daily ultrafiltration, increase in nPNA (from 0.91 to 1.10 g/kg), and increase in percentage of lean body mass (all significant) at 6 months, whereas there were no changes in any parameters in control patients ($Kt/V_{urea} = 1.66$ at month 0 and 1.69 after 6 months). This nonrandomized trial suggests that patients with Kt/V_{urea} less than 1.7 may benefit from intervention. Therefore, frequent collections appear warranted.

LIMITATIONS

There are only 2 randomized trials of dialysis dose in PD patients. The study designs were different in that the ADEMEX Study targeted a higher level of peritoneal clearance (not quite achieved), whereas the Hong Kong trial targeted 3 levels of total Kt/V_{urea}, combining kidney and peritoneal clearance to achieve this and adjusting the PD prescription to stay within the indicated goal. Each study had a homogeneous ethnic population (Mexican and Chinese, respectively). Therefore, the ability to apply these results to different ethnic groups and more culturally heterogeneous populations is limited and is the reason that the evidence is listed as moderate, rather than strong. Of particular concern is the variability in adherence to home prescription in other cultures in which adherence was shown to be problematic in some patients.

Data are limited in anuric patients. There are no randomized trials examining different prescribed and delivered doses of peritoneal small-molecule clearance in completely anuric patients. Slightly more than one half the patients in the ADEMEX Study were essentially anuric and a subanalysis was performed, but the study was not specifically designed to study this population.

There is even less information on levels of prescribed dose for CCPD, and even more limited on APD with dry days. There are no randomized trials comparing different doses on CCPD therapy or comparing CCPD with APD with a dry day. Of particular interest are patients who start PD with APD with a dry day and subsequently have a day exchange, and then 2 day exchanges added, a form of incremental dialysis. Theoretically, this might protect the peritoneal membrane from 24-hour glucose exposure, but middle-molecule clearance would be restricted with such an approach if applied early in the course of PD. In view of the very limited data about APD clearances and outcomes, no guidelines are possible for small-molecule clearance on APD therapy.

There are no randomized trials examining middle-molecule clearances in PD patients. Because emerging data suggest a plateau effect of small-molecule clearances on outcome in both PD and HD patients, attention should be turned to other uremic toxins. For example, there are no randomized long-term trials examining risk for neuropathy with these relatively low levels of PD prescription because this may appear after several years and the present studies examine 2 to 3 years. Longer term trials are necessary.

IMPLEMENTATION ISSUES

The prescribed dose of PD, as is true of HD, is not invariably the delivered dose. Patients adjust the timing of exchanges, eliminate exchanges, and change the dextrose of the dialysis solution, resulting in variations in ultrafiltration that, in turn, affect small-molecule clearance. Patients are responsible for their dialysis delivery, yet depression is common in PD patients, which may impact on adherence.[75,76] Close attention must be paid to the patient's ability to perform (mentally and physically) his or her dialysis.

Furthermore, RKF does not remain stable. It is affected by volume status and tends to decrease over time. Therefore, if including residual kidney clearance as part of total Kt/V_{urea}, the measured dose of Kt/V_{urea} may not precisely reflect the delivered dose of

Kt/V_{urea}, which will be less in some cases. This means that the clinician should err on the side of a higher prescribed dose when possible.

Implementation of the goal of euvolemia in PD patients involves close monitoring of urine volume, ultrafiltration, and physical examination, including blood pressure. Both home records and in-center measurements are needed. Frequent contact with the patient to supervise the use of the appropriate dialysis dextrose solution is necessary. The use of loop diuretics may be indicated to increase urine volume as appropriate (discussed later). "Negative" ultrafiltration with the long exchange should be avoided by adjusting the prescription and dialysate dextrose solution.

COMPARISON TO OTHER GUIDELINES

In 1999, the Canadian Guidelines for Adequacy and Nutrition in PD were published.[77] For CAPD and APD, the minimum weekly Kt/V_{urea} clearance target was set at 2.0. C_{Cr} targets were 60 L/wk in high and high-average peritoneal transporters and 50 L/wk in low and low-average peritoneal transporters. This was given as an opinion. Clearance values for Kt/V_{urea} of 1.7/wk and C_{Cr} of 50 L/wk were considered almost always unacceptable. The recommendation was to perform a collection within 6 to 8 weeks of starting PD therapy and then, ideally, every 6 months, unless the prescription was changed or clinical status changed unexpectedly. A cautionary note was to be aware of the potential for noncompliance with exchanges. Clinic visits were considered to be adequate every 2 to 3 months unless the patient was not doing well. It was recommended to perform a peritoneal equilibration test (PET) within 6 weeks of initiating PD therapy. Special attention should be paid to state of hydration, serum albumin level, and nutritional status in high transporters. The importance of controlling volume overload and hypertension was emphasized.

The draft document from November 21, 2003, of the Canadian Society of Nephrology Clinical Practice Guidelines on PD Adequacy, not yet finalized, indicates that the term "adequacy" must be defined more broadly, rather than limited to only small-molecule clearances. The authors suggest that adequate dialysis includes attention to volume status and nutrition and cardiovascular risk reduction. Focus on preservation of RKF also is necessary. The Canadian draft guidelines contain 6 sections. The first indicates that peritoneal Kt/V_{urea} should be maintained at a minimum of 1.7 per week in both CAPD and APD patients when kidney rGFR is less than 4 mL/min. In patients with GFR greater than 4 mL/min, peritoneal Kt/V_{urea} may be maintained at 1.0 to 1.7. If the patient appears uremic, the peritoneal prescription should be increased. The draft guidelines emphasize the importance of considering lifestyle issues of the patient and caretakers, if any, and the effect of cumulative exposure to glucose. If peritoneal clearance is less than 1.7/wk because of dependence on RKF, the recommendation is to measure GFR every 2 months. Peritoneal Kt/V_{urea} can be measured every 6 months unless there is an unexpected change in the patient's condition. One section in the draft document is devoted to volume status and blood pressure. Emphasis is placed on appropriate prescription (in particular, a reasonable dwell time of at least 2 hours to permit sodium removal) and use of icodextrin and diuretics, as appropriate. If blood pressure is greater than 130/80 mm Hg,

the investigators recommend achieving euvolemia and, if not effective, adding an antihypertensive, giving preference to an angiotensin-converting enzyme (ACE) inhibitor.

The Australian PD guidelines are published online (www.cari.org.au; last accessed 2/14/2006).[77A] As evaluation of adequacy, the guidelines recommend including clinical assessment of well-being, physical measurements, small-solute clearance, fluid removal, and the impact of treatment on the individual's life. Clearances alone (either greater or less than the target) should not be interpreted as representing adequate or inadequate dialysis. For CAPD and APD, weekly Kt/V_{urea} is recommended as 2.0, with a minimum of 1.7/wk. Minimum C_{Cr} target is given as 60 L/wk in high and high-average transporters and 50 L/wk in low-average and low peritoneal transporters. Kt/V_{urea} less than 1.7 and corrected C_{Cr} of 50 L/wk should be considered unacceptable for a patient with a BMI of 20 to 26 kg/m^2. Emphasis is placed on not using small-solute clearance alone, but interpreting results together with clinical and laboratory assessments, including hydration status, blood pressure and lipid control, bone disease, anemia, and nutrition.

The Renal Association (UK) Guidelines, published in August 2002, recommend a total weekly C_{Cr}, combining dialysis and RKF, of 50 L/wk/1.73 m^2 and/or weekly dialysis Kt/V_{urea} of 1.7 or greater (www.renal.org/Standards/RenalStandSumm02.pdf).[77B] These should be measured by 6 to 8 weeks after the start of dialysis therapy and repeated at least annually, more often if RKF is rapidly decreasing. The suggestion is made that high or high-average transporters and APD patients may need higher targets.

The European Best Practice Guidelines for PD were initiated in 1999 and published in 2005.[78] The minimum peritoneal target for Kt/V_{urea} in anuric patients is 1.7, identical to that in the present guidelines, but in addition, the guidelines recommend net ultrafiltration in anuric patients of 1.0 L per day. This guideline is believed to be evidence based (level B). No specific targets are provided for those with RKF other than to note that RKF can compensate when these peritoneal targets are not achieved. A higher Kt/V_{urea} target for APD was not recommended, with the rationale of the rapid diffusion of urea during short cycles, such as occurs with the cycler at night. However, the guidelines recommend achieving a minimum C_{Cr} of 45 L/wk/1.73 m^2, as well as a minimum Kt/V_{urea} of 1.7 in patients on the cycler (evidence level C).

GUIDELINE 3: PRESERVATION OF RESIDUAL KIDNEY FUNCTION

Prospective randomized trials of dialysis adequacy and many observational studies have confirmed a strong association between the presence of RKF and reduction of mortality in patients on PD therapy.

3.1 It is important to monitor and preserve RKF. (A)

3.2 In the patient with RKF who needs antihypertensive medication, preference should be given to the use of ACE inhibitors or angiotensin receptor blockers (ARBs). (A)

3.3 In the normotensive patient with RKF, consideration should be given to the use of ACE inhibitors or ARBs for kidney protection. (B)

3.4 Insults to RKF (see Table 7) in patients with CKD also should be considered insults to RKF in PD patients and should be avoided when possible. (B)

BACKGROUND

Studies of the adequacy of PD, measured by small-solute clearance (Kt/V_{urea} and C_{Cr}), have shown that in the presence of RKF, outcome is driven by the kidney component only. In studies in which both the kidney and peritoneal contribution to small-solute clearance are measured, RR for mortality is related inversely to only the kidney component.[37,41,42,46,79] There is no significant association between peritoneal small-solute clearance and outcome. It is only in studies of anuric patients that peritoneal clearance parameters are associated with outcome,[67,73] and even then, peritoneal ultrafiltration may be more important than peritoneal small-solute clearance.[71] The mechanism(s) involved in the robust association between RKF and reduction in mortality are purely speculative.

One possible benefit of preserved kidney function may be the kidney excretion of salt and water, which helps maintain euvolemia. In the reanalysis of the CANUSA Study, residual urine volume was more important than residual kidney small-solute clearance in predicting outcome.[37] Furthermore, other studies showed that preserved kidney function is associated with both better blood pressure control and maintenance of more normal cardiac geometry.[48,87,88]

Another explanation for the benefit of RKF is that ongoing kidney clearance of uremic solutes contributes in a more significant way to reduction in mortality than that afforded by peritoneal clearance. Why kidney Kt/V_{urea} or C_{Cr} should reduce mortality while peritoneal Kt/V_{urea} or C_{Cr} does not very likely lies in other solutes cleared by the kidneys and perhaps less well-cleared by the peritoneal membrane. In other words, kidney small-solute clearance parameters serve as a marker of ongoing kidney function, but the benefit of the function is in the removal of other unmeasured uremic toxins.

Another possibility is that the association of preserved kidney function and better outcome is not the direct result of any excretory function of the kidney (eg, salt, water, small or large solutes). It may be that intrinsically "healthier" or relatively "uninflamed" patients may have a slower decrease in RKF. Studies have reported comorbid disease to be associated with faster decrease in RKF in patients on dialysis therapy[89]; thus, the

Table 7. Potential Insults to RKF in Patients on Dialysis

Radiocontrast dye administered intravenously or intra-arterially
Aminoglycoside antibiotics
NSAIDS, including cox-2 inhibitors
ECF volume depletion
Urinary tract obstruction
Hypercalcemia
Withdrawal of immunosuppressive therapy from a transplanted kidney

absence of comorbid disease would be associated with relative preservation of kidney function. Therefore, the better outcome in dialysis patients with more preserved kidney function may be a marker of the relative absence of comorbid disease in these patients, rather than a particular life-prolonging function of the kidneys themselves.

Large population studies showing an association between decrease in kidney function and adverse cardiac events have led to the "cardiorenal" hypothesis. This hypothesis states that loss of kidney function increases the chance of cardiac-associated mortality in a manner that is not readily explained by traditional cardiac risk factors, such as lipid disorders. Healthy kidneys are associated with an absence of inflammation, and the increasing incidence of cardiac events with even minor decrements in kidney function may reflect the loss of this antiinflammatory function. This has led to the observation that patients with decreasing kidney function are more likely to die of cardiac causes than to reach CKD stage 5.[90] However, in those who reach the need for dialysis, the association of further decrease in RKF with adverse events may simply reflect the same cardiorenal process, albeit now at the dialytic end of the spectrum of kidney function.

In the absence of certainty about which, if any, aspect of kidney function is associated with the improved outcome, it seems reasonable to try to preserve kidney function for as long as possible in patients on dialysis therapy.

RATIONALE

Definitions

RKF represents the function of the native kidneys or the in situ kidney allograft. *GFR* is estimated by the numerical average of the 24-hour C_{Cr} and urea nitrogen clearance. *Urine volume* is the volume of urine produced in a 24-hour collection period. *Anuric patients* are those for whom 24-hour urine volume is considered insignificant, arbitrarily chosen as 100 mL/d or less. However, as mentioned in Guideline 2, it is unclear at what volume or GFR the contribution of RKF is considered negligible and the patient is functionally anuric.

It is important to monitor and preserve RKF. Although the explanation for the association of preserved RKF with survival is not known (see Background), the association is so robust in studies from around the world that preservation of this

function should be a major objective in the management of dialysis patients. Furthermore, although the benefit of increasing dialytic (HD or PD) clearance appears to plateau eventually,[38,91] no such asymptotic function holds for RKF. The ultimate extrapolation would be to normal kidney function, and survival in this group is many fold greater than in those with no kidney function.[92]

It is reasonable to assume that interventions that slow the decrease in kidney function in patients with CKD also will slow the decrease in RKF in patients on dialysis therapy. Furthermore, agents or events that are nephrotoxic in general can be assumed to be nephrotoxic to RKF. There are different levels of evidence to support these assumptions.

In the patient with RKF who needs antihypertensive medication, preference should be given to the use of ACE inhibitors or ARBs. The last 2 decades have seen a plethora of studies showing that control of blood pressure, particularly by the use of ACE inhibitors and ARBs, is associated with a decrease in the slope of decline in kidney function in patients with kidney disorders, particularly those with diabetic kidney disease or glomerulonephritis.[93–97] In many studies, the salutary effect of ACE inhibitors and especially ARB agents was seen with little or no change in blood pressure control. Again, can the assumption be made that interventions that slow the decrease in GFR in patients with CKD also work in dialysis patients?

A retrospective study of more than 200 PD patients found that patients not administered antihypertensive drugs had a faster decrease in their kidney function.[89] In analysis of data from the USRDS, use of an ACE inhibitor or calcium channel blocker was associated with decreased loss of RKF, defined as urine volume greater than 200 mL/d.[98]

These observations led to 2 RCTs that examined the effect of ACE inhibition and angiotensin receptor blockade on RKF in PD patients. In the first study, 60 PD patients were randomized to receive 5 mg of ramipril or no treatment. Other antihypertensive agents could be used. At the end of 1 year, the subgroup administered the ACE inhibitor had just less than 1 mL/min greater GFR compared with those not administered the drug.[99] A similar study, albeit in even fewer patients, showed that 40 to 80 mg/d of valsartan was associated with a slower decrease in GFR and urine volume at 24 months, without a difference in blood pressure.[100] Although the number of patients in each study was small, there is consistency between the 2 studies and a believable physiological underpinning to the findings. For this reason, the use of these agents is recommended when antihypertensive therapy is indicated for PD patients.

In the normotensive patient with RKF, consideration should be given to the use of ACE inhibitors or ARBs for kidney protection. It is not clear how much of the renoprotective effect of ACE inhibitors or ARBs is related to their antihypertensive effect versus other mechanisms.

Studies of nondialysis populations suggested that the renoprotective effect is, in part, independent of effects on blood pressure. Therefore, these agents often are used in patients with CKD, especially those with glomerulonephritis or diabetic kidney disease, even if the patients are normotensive. If this effect can be extrapolated to patients on dialysis therapy, it would suggest that these agents can slow the decrease in kidney

function even in those with normal blood pressure. In both studies of ACE inhibitors and ARBs, the salutary effect of the drugs on RKF was independent of changes in blood pressure.[99,100] One study specifically targeted patients with a blood pressure of at least 120/70 mm Hg.[99] Although average entry blood pressure was high, it is not clear whether normotensive patients were involved in these studies and whether the agents had an effect in this subset of patients (Table 8).

Insults (Table 7) to RKF in patients with CKD also should be considered insults to RKF in PD patients and should be avoided when possible. Other drugs, events, and interventions that worsen kidney function in patients with CKD also should be expected to worsen RKF in patients on dialysis therapy. Potential insults are listed in Table 7; this list should not be considered all inclusive. Whereas it is reasonable to make the assumption that exposure to these potential nephrotoxins might harm RKF in PD patients, there is little high-grade evidence to prove it.

Retrospective analyses of RKF found that previous episodes of PD peritonitis are associated with faster kidney decline.[89,101] This could be the result of the inflammation of the peritoneum itself, drugs used to treat the infection, or associated ECF volume depletion. A general linear multivariate model also implicated the use of aminoglycosides, separate from the rate of peritonitis, as an associated factor.[89] A retrospective study of RKF found that patients for whom peritonitis was treated with aminoglycosides had a greater decrease in kidney function compared with those treated with other less-nephrotoxic antibiotics.[102] However, the most recent retrospective analysis could not detect a difference in the slope of decrease in GFR in PD patients with peritonitis treated with or without gentamicin.[103] The data therefore are not strong and are somewhat contradictory. However, if an antibiotic without the nephrotoxic potential of an aminoglycoside can be used in its place without compromising antibacterial efficacy, it is still recommended to do so.

Other agents that should be avoided are nonsteroidal anti-inflammatory drugs (NSAIDs), including cyclooxygenase-2 (COX-2) inhibitors. These drugs may be particularly harmful under conditions of preexisting kidney insufficiency or diminished kidney blood flow. This setting, of course, applies to RKF in patients on dialysis therapy; thus, this may represent a group particularly vulnerable to the nephrotoxic effects of COX-2 inhibitors. Conventional analgesia, such as acetaminophen, should be used in dialysis patients with noninflammatory pain. Other drugs to consider are low-dose opiates (watching for constipation) and short courses of oral or intra-articular corticosteroids for acute inflammatory noninfectious arthritis.

Intravenous or intra-arterial dye can be nephrotoxic, especially in patients with antecedent kidney dysfunction, particularly diabetic nephropathy. Again, there is no reason to expect that this risk is less for RKF in patients on dialysis therapy. In dialysis patients with kidney function, the decision to administer a dye load should not be taken lightly. The indication for the dye study should be reviewed, and alternative studies that do not use dye should be sought. The patient who must undergo the study should be well hydrated at the time, and the smallest volume of the least nephrotoxic dye should be used.

Table 8. Effect of Pharmacological Interventions on Residual Kidney Function

Author, Year	Design	N	Follow-up (Maximum)	Applicability	Intervention	Outcome	Results Multivariate	Quality
Aminoglycosides								
Singhal, 2000[83]	Prospective cohort	242	27 mo	↑↑↑	Aminoglycosides >5 d at least once vs. none	GFR decline (slope), comparison of highest and lowest quartiles (overall -0.04 mL/min/mo decline, y intercept 4.5 mL/min)	P = 0.0006	○
Shemin, 1999[102]	Prospective cohort	72 (Peritonitis)	14 mo	↑↑	Aminoglycosides >3 d vs. none	C_{Cr} change (mL/min/mo)	-0.66 vs. -0.21 P <0.01	○
						Daily urine output change (mL/d/mo)	–74 vs. –15 P<0.01	
Baker, 2003[103]	Prospective cohort with historical control	205 (Peritonitis)	nd	↑↑	Gentamycin vs. none	GFR change (mL/min/mo)	-0.08 vs. -0.17 NS	○
						Daily urine output change (mL/d/mo)	-8.8 vs. -34.7 NS	
ACEI/ARB								
Li, 2003[99]	RCT	60	(12 mo)	↑	Ramipril 5 mg daily vs. other antihypertensive (BP <135/85)	Residual GFR change (mL/min per 1.73 m²)	-2.07 vs. -3.00 P = 0.03	◉
						Anuria	HR = 0.58 (0.36-0.94) P <0.05	
Johnson, 2003[111]	Prospective cohort	146	21 mo	↑↑↑	ACEI vs. no ACEI	RKF decline	HR = 0.81[a] (0.52-1.27) NS	◉
Singhal, 2000[83]	Prospective cohort	242	27 mo	↑↑↑	ACEI vs. none	GFR decline (slope), comparison of the highest and lowest quartiles	-0.14 vs. -0.16 NS	○
Moist, 2000[98]	Retrospective cohort	1,032	(18 mo)	↑↑↑	ACEI vs. no ACEI	Time to anuria	OR = 0.70 P = 0.02	○

a. Univariate analysis.

Whether pretreatment with *N*-acetylcysteine is helpful in decreasing the incidence and severity of dye nephrotoxicity is controversial in patients with CKD; there are even fewer data for patients on dialysis therapy.[104,105] Furthermore, there are no studies examining volume expansion as a method of protecting RKF in patients on dialysis therapy who must undergo contrast studies. However, given the low cost and favorable side-effect profile of *N*-acetylcysteine, consideration should be given to pretreating patients with this agent before the dye study, and it also would seem reasonable to ensure that volume depletion is not present.

As in any patient with unexplained deterioration in kidney function, both prekidney and postkidney causes should be ruled out. Given that the mean age of patients starting dialysis therapy is increasing, prostatic hypertrophy with urinary obstruction must be considered in men with sudden deterioration in function. Episodes of ECF volume depletion are associated with a decrease in urine volume and function[106,107] and should be avoided unless necessary to keep the patient out of CHF.

PD is associated with low bone turnover. In PD patients, there is a good chance of hypercalcemia as a result of aggressive therapy with oral calcium or calcitriol and vitamin D analogs. The resulting increase in serum calcium concentration could be nephrotoxic; thus, hypercalcemia should be avoided.

Finally, many patients who start on (or return to) PD therapy after a "failed" kidney transplant have significant residual function in the transplanted kidney. It is unclear whether patients should continue to receive immunosuppressive therapy, particularly with agents other than calcineurin inhibitors, in an attempt to prolong this RKF. A recent decision analysis suggested that the benefit of continued immunosuppression outweighed the risk when C_{Cr} was greater than approximately 1.5 mL/min.[108] However, this conclusion remains to be validated by clinical studies.

IMPLEMENTATION ISSUES

Whether urine volume, small-solute clearance, or some other kidney-related factor is responsible for the decrease in mortality associated with RKF, it is important to have some measure of this residual function. It is impracticable to use exacting tests to calculate this, such as inulin clearance or radionucleotide measurements. The average of urea nitrogen and C_{Cr} has been shown to have a reasonable approximation of RKF.[109] However, the accuracy of this measurement depends on the careful collection of 24-hour urine. Especially in patients with very little function, inaccuracy in the timing of the collection can lead to incorrect results. Accuracy perhaps can be improved by the collection of a 72-hour sample and dividing the result by 3[110]; however, this is a time-consuming and cumbersome process. Patients will need to be instructed on the careful collection of 24-hour urine and make it a habit to bring these collections as part of the regular clinic visit.

Use of ACE inhibitors and ARBs may add to the cost of medications for patients. In addition, there is a risk for cough, particularly with ACE inhibitors. There also is a theoretical risk for hyperkalemia, although this has not been found in studies to date.

GUIDELINE 4. MAINTENANCE OF EUVOLEMIA

Volume overload is associated with CHF, left ventricular hypertrophy (LVH), and hypertension; therefore, it is important to monitor ultrafiltration volume, dry weight, sodium intake, and other clinical assessments of volume status.

4.1 Each facility should implement a program that monitors and reviews peritoneal dialysate drain volume, RKF, and patient blood pressure on a monthly basis. (B)

4.2 Some of the therapies one should consider to optimize extracellular water and blood volume include, but are not limited to, restricting dietary sodium and water intake, use of diuretics in patients with RKF, and optimization of peritoneal ultrafiltration volume and sodium removal. (B)

BACKGROUND

There is a high prevalence of coronary artery disease, LVH, and CHF in patients with CKD stage 5, including those on PD therapy.[112] Cardiovascular disease (CVD) is the largest cause of death in this population.[112] In the general population without kidney failure, hypertension is a major risk factor for all these conditions.[113] In patients with kidney failure, the literature is less clear, but volume overload is widely believed to be the major contributor to hypertension.[114] Therefore, interventions to optimize volume status (and hence blood pressure) are considered central to the management of these patients.

RATIONALE

There are no RCTs addressing the effect on survival of interventions to improve blood pressure and volume control in PD patients, but there is broad consensus, based on the general cardiovascular literature, that normalization of blood pressure and volume status in these patients is desirable.

There is circumstantial evidence from observational studies suggesting that better volume control may improve outcomes. This evidence includes the finding in a number of studies that low transport status according to PET is associated with improved outcome in CAPD patients; this may reflect the beneficial effect of low transport status on peritoneal ultrafiltration and thus on clinical outcome.[36,81] Greater fluid removal (peritoneal plus kidney) also was found to be a favorable predictor of outcomes in observational studies of both CAPD and APD patients; again, interpretation of this finding remains controversial because it is unclear whether greater fluid removal indicates better or worse control of volume status or it is just a marker of fluid intake.[48,71,115] The relationship between blood pressure and survival in patients with CKD stage 5 is confounded by the high prevalence of cardiac failure, which is associated with both hypotension and greater mortality.[116] However, 1 study found that hypertension is associated with a greater likelihood of de novo cardiac failure in patients with CKD stage 5 treated with HD.[117]

Each facility should implement a program that, each month, assesses patients' blood pressure and volume status and evaluates their drain volume, RKF, and dietary salt and water intake. To ensure good control of blood pressure

and volume status in PD patients, clinical examination of the patient needs to be carried out on a monthly basis. Less frequent examination may be acceptable. An approach to the volume overloaded patient has been developed by the International Society for Peritoneal Dialysis and was published elsewhere.[218] In particular, this should involve reevaluation of the patient's target weight. Clinical examination will need to be done more frequently in the initial weeks of PD therapy when target weight is being established for the first time. In stable well-established PD patients with well-controlled blood pressure, less frequent examination may be acceptable.

Key determinants of volume status in PD patients are salt and water intake, RKF, and net peritoneal fluid removal; these also should be reviewed on a monthly basis. Salt and water intake is not routinely restricted in PD patients, but should be evaluated if there is persistent volume overload and hypertension. This can be done by a dietitian or indirectly by measuring salt and water removal by RKF and PD.

Salt and water removal are evaluated by measuring daily urinary volume and sodium content and measuring the difference between the volume and sodium content over 1 day of the dialysate effluent and infused dialysis solution. In this calculation, it is important to remember that PD solution bags routinely are overfilled to allow for flushing of the tubing before infusion of fluid into the peritoneal cavity.[118] Total sodium and water removal by peritoneal and urinary routes can be considered a reasonable indicator of sodium and water intake, provided the patient is clinically stable and sodium and water losses by other routes are taken into account.

Particular attention should be given to the net peritoneal fluid absorption that frequently occurs with long duration dwells, such as the nocturnal dwell in CAPD and diurnal dwell in APD, because this can be avoided by altering the PD prescription.

Some of the therapies one should consider implementing to optimize extracellular water and blood volume include, but are not limited to, restricting dietary sodium and water intake, use of diuretics in patients with RKF, and optimization of peritoneal ultrafiltration volume and sodium removal. As discussed, dietary advice can be given to reduce sodium and water intake in the event of a persistent problem with hypertension and/or fluid overload. In patients with RKF, a small RCT showed that urinary sodium and water removal can be enhanced, or at least maintained for longer, on PD therapy and that volume status can be improved with the use of high-dose loop diuretics.[119] Other RCTs also showed urinary volume and clearance to be maintained better in patients treated with ACE inhibitors and also those treated with ARBs.[99,100]

Peritoneal fluid removal can be increased by using a more hypertonic glucose solution or an alternative osmotic agent, such as icodextrin. Consistent use of hypertonic glucose solutions raises concerns about damage to the peritoneal membrane and the adverse effects of increased systemic absorption of glucose. Concerns about the role of glucose in membrane deterioration, in particular, have been supported by recent studies.[120,121] A preferred approach is to avoid long-duration dwells that often are associated with ineffective fluid removal or even net fluid resorption. In patients on APD therapy, this can

be done by either shortening the day dwell and leaving the patient "dry" for a portion of the day or draining out the day dwell and replacing it with fresh dialysis solution partway through the day. In CAPD patients, it can be dealt with by switching to APD without a long day dwell or using a night-exchange device to divide the nocturnal dwell into 2 shorter dwells. An alternative strategy is to use icodextrin solution for the long nocturnal dwell in CAPD patients and the long day dwell in APD patients. This was shown in RCTs to both increase peritoneal ultrafiltration and decrease ECF volume.[122,123] With icodextrin in place, there is no need to drain a day dwell early to optimize ultrafiltration. However, some patients may still request a shorter duration day dwell (6 to 8 hours) to allow for a period of day dry time, which some find more comfortable.

LIMITATIONS

While individual strategies—such as loop diuretics, ACE inhibitors, ARBs, and icodextrin—have been shown to increase fluid removal and decrease ECF volume in small RCTs, there have been no trials of sufficient size to examine whether these interventions impact on key patient outcomes, such as patient survival, technique survival, cardiovascular events, hospitalization, and QOL. The likelihood of such studies being done is compromised by the large numbers of patients that would be required to achieve statistical power to answer these questions and by the already widespread acceptance and use of the strategies concerned.

With regard to studies that have been done, use of fluid removal as an end point should be questioned because it is possible that greater fluid removal may simply lead to greater fluid intake without a change in ECF volume status or blood pressure. More weight therefore should be given to studies that use direct and indirect measures of volume status as end points, such as echocardiographic indices, blood pressure, body composition, and body compartment volume estimates.

The whole approach of "optimizing" blood pressure and volume status as a means of improving patient outcome also has not been validated in randomized trials and is justified only by reference to the beneficial effect of decreasing blood pressure that is evident from multiple studies of patients without kidney failure. Again, this strategy is so widely accepted and practiced that it is unlikely to be tested in the PD or CKD stage 5 population in a randomized trial. However, there is a case to be made for carrying out RCTs comparing more- and less-aggressive approaches to decreasing blood pressure because there is no consensus about what appropriate blood pressure targets are in the PD population. There also is little evidence about which antihypertensives are best to use to optimize blood pressure after volume status has been normalized, although benefits shown for high-dose loop diuretics, ACE inhibitors, and ARBs support a primary role for these agents.[99,100,119]

The question of whether greater use of hypertonic glucose damages the peritoneal membrane has been controversial for many years. Recent clinical studies have strengthened the evidence for this hypothesis, but it is not conclusively proven because studies are not randomized and potentially are confounded by such factors as RKF and inflammation.[120,121] The question of whether more use of hypertonic glucose causes greater systemic harm to the patient with more hyperglycemia, hyperlipidemia, hyperinsulinemia,

obesity, and consequent cardiovascular effects has been more difficult to answer, although it might appear intuitively logical that this is the case. In this situation, an appropriate response would be to give the patient the benefit of the doubt and minimize hypertonic glucose exposure while at the same time ensuring that this is not at the expense of volume overload and hypertension. Such a compromise would involve judicious use of salt and water restriction, loop diuretics, and nonglucose PD solutions.

Some cautions have been voiced concerning sodium and water removal in patients on APD. In some patients who are performing multiple short overnight dwells (>4 exchanges over 8 hours) the sodium sieving effect of short-duration APD cycles, as well as the tendency for salt and water resorption during the long day dwells may compromise BP and volume control with this modality.[124,125] One study suggested superior SBP control with CAPD compared with APD therapy.[125] However, this was not a randomized study and previous studies, including a randomized study, did not show worse outcomes on APD therapy.[126] Also, although blood pressure likely is an important surrogate or intermediate outcome, it is not clear that salt and water removal is.[115] It is important to note that blood pressure control is multifactorial. Control of blood pressure and euvolemia can be obtained in patients on APD if the prescription is individualized with attention to the UF profile on the long dwell and minimization of sodium sieving during overnight dwells. Possible maneuvers to minimize this problem include: using less than four overnight exchanges during 8 hours (average in the United States is currently less than 4 exchanges/night time); shortening the day dwell by draining and either doing an additional midday exchange or having a "dry time" with no dialysate present; or by substituting icodextrin for glucose solutions. At present, there is insufficient evidence to justify recommending one PD modality over another, but it would be reasonable to pay close attention to volume status and blood pressure in APD patients.

IMPLEMENTATION ISSUES

Implementation of these guidelines requires patients to have regular clinic visits and physical examinations. These generally should be monthly after the patient is established on PD therapy, but should be more frequent during and in the first weeks after initial training. Less frequent visits may be acceptable if the patient is stable on PD therapy with good blood pressure and volume status.

Access to dietitian assistance will be required to assess and advise patients about sodium and fluid intake. Use of icodextrin requires access to this solution, which is not available in some jurisdictions and which is limited by cost considerations in others.

GUIDELINE 5: QUALITY IMPROVEMENT PROGRAMS

The continuous quality improvement (CQI) process has been shown to improve outcomes in many disciplines, including CKD stage 5.

5.1 Each home-training unit should establish quality improvement programs with the goal of monitoring clinical outcomes and implementing programs that result in improvements in patient care. (B)

5.2 Quality improvement programs should include representatives of all disciplines involved in the care of the PD patient, including physicians, midlevel practitioners, nurses, social workers, dietitians, and administrators. (B)

5.3 Suggested domains of clinical activities one should consider monitoring are listed in Table 9. (B)

BACKGROUND

It is important that each facility establish a CQI program because such programs have been shown to improve outcomes in a variety of disciplines, including the care of patients with CKD stage 5. The domains to be examined need to be considered carefully at each facility. Areas that present particular problems at an individual facility should receive special attention. Because the CQI program will involve review of patient-related activities from a variety of domains, it is important that representatives of all disciplines involved in the care of PD patients (physicians, nurses, social workers, dietitians, and administrators) be included in the CQI process.

There are certain special domains that should be considered for CQI examination for PD facilities, outlined in Table 9. These domains are in addition to the standard therapeutic targets outlined in other parts of the KDOQI Guidelines, which include adequacy measures, blood pressure and volume control, anemia and bone mineral metabolism management, lipid control, etc.

Technique failure is an important issue for PD facilities.[127–129] Technique failure is defined as patients discontinuing PD for reasons other than death or transplantation. It accounts for a variable percentage of the reasons that patients terminate PD therapy. The most common reasons reported for technique failure include peritonitis, catheter-related problems, psychosocial factors, and problems with ultrafiltration or poor clearances.[127–129] Programs are encouraged to evaluate the reasons that patients terminate PD therapy and then develop strategies for improving outcomes.

Peritonitis remains a leading cause of morbidity for PD patients and has been associated with mortality, hospitalizations, and termination of PD therapy.[130–132] Although peritonitis rates have improved significantly during the past several years, peritonitis remains a major issue for PD units. It is important for facilities to develop strategies for tracking peritonitis rates, assessing the organisms responsible for peritonitis, and developing strategies to better understand the reasons for peritonitis. In addition, treatment guidelines for peritonitis have been established by the International Society of PD.[130] Each facility needs to evaluate which treatment strategy is best for its program;

Table 9. Various Domains To Be Considered for CQI Studies

1.	Peritonitis rates
2.	Exit-site infection rates
3.	Technique failure rates
4.	Patient satisfaction
5.	QOL
6.	Catheter-related problems and catheter survival rates
7.	Other domains, outlined in other parts of these guidelines, such as adequacy measures, anemia and bone and mineral metabolism management, blood pressure and volume control, lipid control, etc.

this depends on understanding the rate of peritonitis, organisms causing peritonitis, and possible reasons for peritonitis.

Exit-site infections are a problem for PD patients because these infections may be responsible for peritonitis and lead to catheter removal.[133–135] Treatment guidelines have been developed for the management of exit-site care and infections.[133,134] Facilities should evaluate their exit-site infection rates and review whether their treatment practices provide acceptable levels of care.

A variety of catheters and insertion methods have been used for PD patients. There is insufficient evidence to recommend one type of catheter or one catheter placement technique.[136] Each facility should examine catheter success rates and methods of catheter insertion and track these results over time.

QOL assessments for dialysis patients have been the focus of several studies. A variety of instruments have been used for these assessments; there is no generally agreed-upon or accepted instrument to perform these assessments. However, it should be noted that various findings on these QOL assessments have correlated significantly with morbidity and mortality rates in patients with CKD stage 5 maintained on both HD and PD therapy.[137–141] Monitoring QOL may be particularly important for a home-based therapy.[142] This is especially so because PD therapy is associated with significant technique failure rates and requires patient cooperation and compliance. It should be noted that QOL assessments may present problems in terms of using standardized instruments in geographically, linguistically, and culturally different groups. Although some domains of QOL problems are amenable to therapy,[76,143] it has not been shown that interventions to improve QOL decrease adverse clinical outcomes.

Patient satisfaction with therapy for CKD stage 5 also has been attracting increased attention recently.[144,145] As treatment options for patients with CKD stage 5 expand, it is important to monitor how patients feel about their treatment and their facility so that appropriate modifications can be made to improve patients' perceptions of their therapy and care. This is an important issue to consider for all patients, but is particularly relevant for patients on a home-based therapy, for whom adequate communication between the staff and the patient is essential. There are no generally agreed-upon instruments to assess patient satisfaction with care, but facilities are encouraged to consider examining methods of evaluating this domain.

LIMITATIONS

Although CQI programs generally are considered to be beneficial, there are no studies of PD facilities that document the efficacy of such programs on improving patient outcomes.

The institution of effective CQI programs requires that adequate information be made available and resources be provided to the facility to effectively manage these programs. It is important for the facility to strive to provide the materials necessary to permit CQI programs to operate effectively.

Some of the areas suggested for CQI activity in Table 9 do not have established standards or instruments to assess these domains (eg, patient satisfaction, QOL). Several studies attempted to assess these domains, and each facility will need to review these studies and select instruments that it believes are appropriate.

INTRODUCTION

The provision of evidence-based pediatric PD adequacy guidelines is hampered by a number of epidemiological issues. CKD stage 5 remains a relatively uncommon disease in children, while kidney transplantation is still the predominant mode of KRT. In addition, HD is a viable modality option for many pediatric patients, especially adolescents. 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 similar to the ADEMEX Study is adequately powered to detect an effect of the delivered PD dose on pediatric patient outcome.[38] Nevertheless, pediatric data exist, for example, to describe the most accurate methods for assessing peritoneal membrane transport capacity and quantifying urea removal.[146–148] These data and others can serve as a basis for CPGs in children receiving PD. For areas in which no pediatric-specific data exist, the CPGs and CPRs for adult patients should serve as a minimum standard for pediatric patients, but the overall clinical "wellness" of the individual pediatric patient should be the primary factor that influences the quantity and quality of the care provided.

6.1 Recommended laboratory measurements for peritoneal membrane function:

6.1.1 The PET is the preferred approach to the clinical assessment of peritoneal membrane transport capacity in pediatric patients and should be performed to aid in the prescription process. (A)

6.2 Maintenance of euvolemia and normotension:

6.2.1 The frequent presence of hypertension and associated cardiac abnormalities in children receiving PD requires strict management of blood pressure, including attention to fluid status. (A)

6.3 Quality improvement programs:

6.3.1 The CQI process has been shown to improve outcomes in many disciplines, including CKD stage 5. (A)

6.3.1.1 Each home training unit should establish quality improvement programs with the goal of monitoring clinical outcomes and implementing programs that result in improvements in patient care. In children, growth and school attendance/performance are clinical activities to be monitored in addition to those recommended for adult patients.

6.3.1.2 Quality improvement programs should include representatives of all disciplines involved in the care of the pediatric PD patient, including physicians, nurses, social workers, dietitians, play therapists, psychologists, and teachers.

6.3.1.3 Single-center trends in pediatric clinical outcomes should be compared with national and international data.

RATIONALE

Recommended Laboratory Measurements for Peritoneal Membrane Function

The PET is the most common technique used clinically in children to assess peritoneal membrane transport capacity and guide the prescription process, although other means of membrane assessment have been reported.[146,147,149] Addition of a volume marker during the PET also can provide valuable information regarding fluid handling. Institution of a standardized PET procedure for children has resulted from recognition of the age-independent relationship between BSA and peritoneal membrane surface area and the resultant recommendation for use of a test exchange volume scaled to BSA when one conducts studies of peritoneal transport kinetics in children.[150–152] Based on 2 large-scale studies and resultant normative data, the PET in children should be performed with an exchange volume of 1,000 to 1,100 mL/m^2 BSA.[146,147] Provision of a smaller volume characteristically results in more rapid equilibration of solute between blood and dialysate and the artifactual appearance of an inherently increased (more rapid) membrane transport capacity.[153] Repeated PET testing is recommended when knowledge of the patient's current membrane transport capacity is necessary for determination of the patient's PD prescription (eg, in the setting of suboptimal clearance), especially when clinical events have occurred (eg, repeated peritonitis) that may have altered membrane transport characteristics.[154,155] Kinetic modeling programs have been developed that use peritoneal membrane transport test data from the standard PET and PD capacity (PDC) tests to help in prescription management. These have been validated for clinical use in pediatrics.[151,156]

Maintenance of Euvolemia and Normotension

Hypertension is a common complication of children receiving dialysis. As delineated in the KDOQI CVD Guidelines, determination and management of blood pressure in children should follow recommendations by the Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents.[157,158] In that report, it is recommended that the optimal (normal) SBP and DBP should be less than the 90th percentile for age, sex, and height.

A recent analysis of data from the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) found that 56.9% of nearly 4,000 dialysis patients had uncontrolled hypertension (blood pressure $>$ than the age-, sex-, and height-specific 95th percentile) and an additional 19.7% of patients had controlled hypertension (blood pressure $<$ the 95th percentile with antihypertensive medication).[159] In addition, marked echocardiographic changes have been documented in pediatric patients at both the initiation of dialysis therapy and during maintenance dialysis therapy. A retrospective study of 64 long-term dialysis patients found that 48 children (75%) had LVH, including 26 of 38 children (68%) on PD therapy.[160] Similarly, another report showed increased left ventricular mass (LVM) and LVMI in children receiving dialysis compared with a healthy population.[161] Whereas the cause of the elevated blood pressure is multifactorial, others found that high blood pressure and cardiac impairment were most frequent in the younger and

nephrectomized dialysis patients for whom volume overload appeared to be the most important etiologic factor.[162]

Proper fluid management requires knowledge and repeated monitoring of the patient's daily residual kidney volume and daily ultrafiltration volume. Efforts to modify the dialysis prescription with the goal of enhancing ultrafiltration with the lowest possible dialysate dextrose concentration are conducted best with knowledge of the patient's peritoneal membrane transport capacity as derived from the PET. If patients are characterized as high/rapid transporters and are unable to achieve the ultrafiltration necessary for blood pressure control with standard dialysis solutions, consideration should be given to the use of an icodextrin-based dialysis solution.[163,164] Whereas its use has been associated with enhanced ultrafiltration in pediatric patients, a recent report suggests that icodextrin-associated fluid removal correlated significantly with age and that icodextrin may behave differently in young children in whom ultrafiltration may not be as successful.[165] This experience has not been duplicated in other centers and requires confirmation.

Recommendations for antihypertensive therapy in children are provided in the Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents, as well as in the KDOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in CKD.[157,166]

Finally, in some patients who are polyuric, negative net daily ultrafiltration may be desirable because of its potential to replenish decreased intravascular volume and improve RKF. When negative net daily ultrafiltration is not possible, provision of additional fluids is recommended.

Quality Improvement Programs

A CQI program should be instituted in all dialysis facilities that care for children receiving PD, based on evidence that improvements in patient care are best achieved in this manner. In addition to monitoring outcomes related to, for example, complications related to infection, achievement of solute clearance targets, adequacy of nutrition, osteodystrophy, anemia management, and QOL, school attendance/performance and growth are key issues to be monitored in any program caring for children receiving long-term dialysis. Not surprisingly, data collected by the NAPRTCS showed that children receiving PD regularly show better school attendance than those on HD therapy.[167] However, differences exist in the PD population when attendance is stratified by race, an issue that requires attention and often intervention. The recommendation for regular growth assessment, as previously delineated in the pediatric component of the KDOQI Nutrition Guidelines, results from the negative impact that CKD can have on height velocity and the association between poor growth and poor outcome in children receiving dialysis.[35,168] The use and influence of medical interventions (eg, correction of acid-base abnormalities, control of secondary hyperparathyroidism and renal osteodystrophy, provision of adequate nutrition, and institution and effect of recombinant human growth hormone therapy) also should be monitored.[168A–171]

Although programs with varying levels of pediatric expertise coordinate the care of children receiving long-term dialysis, ideally, a treatment facility should be able to provide the

necessary multidisciplinary services required by children and families through a team of specialists with pediatric experience. All these disciplines should be involved in the CQI process.[172]

In view of the relatively small number of children who receive PD in any one center, it is imperative that single-center data be compared with results contained in large pediatric databases to determine whether modification of a center's program is deemed necessary. Organizations such as the NAPRTCS and USRDS provide such data.[24,173]

LIMITATIONS

Although attention to fluid management likely will benefit blood pressure control and help prevent the development of CVD in children receiving PD, no large-scale study of the pediatric CKD stage 5 population has proved this to be true.

Although CQI programs generally are considered to be beneficial, there are no studies of pediatric PD facilities that document the efficacy of such programs in terms of their ability to improve patient outcomes.

While it is intuitively beneficial for the CQI program to be multidisciplinary in nature, quality standards for some disciplines in terms of their application to the pediatric PD population have not yet been established.

II. Clinical Practice Recommendations for Peritoneal Dialysis Adequacy

CLINICAL PRACTICE RECOMMENDATION FOR GUIDELINE 1: INITIATION OF KIDNEY REPLACEMENT THERAPY

There is variability with regard to when a patient should be started on dialysis.

1.1 Kidney replacement therapy may be started earlier for a variety of reasons, as outlined in Table 10.

Table 10. Indications for Early Dialysis Start

Intractable fluid overload
Intractable hyperkalemia
Malnutrition felt to be related to uremia
Uremic neurological dysfunction
Uremic serositis
Declining functional status otherwise unexplained
Prediction of access difficulty

1.2 Uremic cognitive dysfunction can affect learning. Therefore, the initiation of home-based self-dialysis may need to occur at an earlier point than that for center-assisted dialysis.

1.3 Kidney replacement therapy may be delayed if the patient is asymptomatic, is awaiting imminent kidney transplant, is awaiting imminent placement of permanent HD or PD access, or, after appropriate education, has chosen conservative therapy.

1.3.1 If KRT is delayed, the patient should be re-evaluated on a regular basis to determine when KRT should be initiated.

1.3.2 Nephrologists should actively participate in the care of patients who choose conservative therapy, and should consider conservative treatment of kidney failure as an integral part of their clinical practice.

1.3.3 If, for any reason, KRT is not instituted, patients with estimated GFR <15 mL/min/1.73 m2 should be re-evaluated by a nephrologist at frequent intervals.

1.4 Choice of modality:

1.4.1 Patients who choose PD for their modality should not be required to have a HD access placed. However, venous sites for possible future HD access in the arms should be preserved since many patients require multiple modalities during their remaining lifetime.

1.4.2 Patients who chose cycler dialysis for lifestyle reasons can begin dialysis without an intervening period on CAPD; however, some programs may wish to train all patients on the CAPD technique for various reasons.

1.5 In the patient with significant RKF, consideration may be given to an incremental start of dialysis, i.e., less than a "full" dose of PD.

RATIONALE

Kidney replacement therapy may be started earlier for a variety of reasons (see Table 1). Patients with advanced cardiomyopathy have been initiated on dialysis at a GFR greater than 15 mL/min successfully. Such an approach may decrease the length of hospitalizations and improve QOL.173a-173f There are no data that this may prolong survival, but an improvement in QOL would seem sufficient to utilize this approach.

In 2000, NKF KDOQI published clinical practice guidelines addressing the management of nutrition in CKD.35 These guidelines updated and partially revised the DOQI Peritoneal Adequacy Guidelines of 1997 that recommended the imitation of dialysis based on nutritional deterioration due to uremia. Also in 2000, the PD Adequacy Work Group revised its 1997 Guidelines to include as its Guideline 2, the verbatim Guideline 27 of the Nutrition Guidelines specifically describing the imitation of dialysis based on nutritional indications.35 The 2005 PD Adequacy Work Group recognizes these previous guideline and refers readers to them. Since 2000, any publications addressing this issue have corroborated the earlier observations as described in the 2000 Nutrition Guidelines.

Uremic cognitive dysfunction can affect learning. Therefore, the initiation of home dialysis may need to occur at an earlier point than that for center-assisted dialysis. The patient who chooses home dialysis, whether it be home HD, cycler PD, or CAPD, generally is the one who is to learn the procedure. Therefore, it becomes important to plan the start of dialysis carefully such that the patient is not so sick that he or she cannot adequately learn the procedure. If this is not done properly, the patient will require a period of time on in-center HD. This is undesirable for a number of reasons. First of all, this often means the patient will have a HD catheter, which is a very significant risk factor for bacteremia (a much higher risk than a PD catheter). Secondly, the time on HD may impair RKF. Thirdly, this may strain the resources of the HD program. Planning for training also requires coordination with the home-training nurses, as there may be limited resources available. In some cases (e.g., children, or those with a helpful and willing spouse), the learner is someone who is not uremic. In these cases, it is not quite as important to begin the training early.

Kidney replacement therapy may be delayed if the patient is asymptomatic, is awaiting imminent kidney transplant, is awaiting imminent placement of permanent HD or PD access, or, after appropriate education, has chosen conservative ther-

apy. If KRT is delayed, the patient should be re-evaluated on a regular basis to determine when KRT should be initiated. Given the risk of starting dialysis with a tunneled HD catheter, if the patient is completely asymptomatic and access placement is imminent, it would seem reasonable to delay the start of dialysis until more permanent access can be placed, either an arteriovenous fistula or PD catheter. Some patients refuse the option of dialysis and are not suitable transplant candidates. Such patients may change their minds as kidney failure progresses and symptoms increase. Therefore, it is important to closely follow such patients.

Patients who choose PD for their modality should not be required to have a HD access placed. Many patients who start PD have, as their ultimate goal, kidney transplantation. As such, the patient may be on PD only a relatively short time (measured in years) prior to transplantation. It would seem unreasonable in such cases to expose the patient to the risk of placement of HD access. For those patients who appear likely to fail PD in the future, formation of an arteriovenous fistula in a timely manner may appear reasonable; however, there are limited data on who might be at risk for PD failure.

Patients should not be required to first train for CAPD if planning to perform cycler therapy at home. After receiving information about PD, patients often have strong opinions on whether they prefer CAPD or the cycler for home dialysis. In some cases the cycler is chosen because of convenience, work schedule, or because a partner is helping the patient. Thus, if this is the patient's modality choice, it would seem reasonable to train the patient on the cycler from the start. The program may chose to subsequently train the cycler patients on manual exchanges as a back-up plan if electricity fails, or if a mid-day exchange is added.

In the patient with significant RKF, consideration may be given to an incremental start of dialysis, i.e., less than a "full" dose of PD. A working definition of incremental dialysis is the addition of any type of dialysis in defined doses over time to achieve a prescribed total clearance which is achieved by the combination of dialysis plus RKF. It can refer to the addition of one type of dialysis to another as well as any type of dialysis to RKF.[173g,173h] This concept has been utilized for a long time and can be considered individualization of therapy by mixing and matching therapies to a specific set of circumstances. The stage was set for this approach in 1985,[173i] and numerous variations have been applied with success since.[173j-173n] The original 1997 DOQI Peritoneal Adequacy Guidelines endorsed this approach in the correct setting. In particular, patients have to understand the concept and clearly intend to comply with the addition of greater dialysis doses as RKF declines. This is addressed in the education program described above and, in the case of home dialysis, further accentuated during the home-training process. There may be logistical (e.g., travel distance), economic, psychological, social, or even medical reasons to attempt incremental dialysis. It is feasible and well described, but may not be suitable for all patients. Furthermore, some clinicians feel that more dialysis is better than less, regardless of RKF, so they recommend full-dose dialysis from the onset.

LIMITATIONS

The data are very limited in many of the areas discussed. For example, intractable volume overload in patients with cardiomyopathy may be managed with isolated ultrafiltration. This approach would appear to have significant risk to RKF. Studies comparing peritoneal approaches, such as using a single exchange with icodextrin for such patients, to isolated repeated ultrafiltration have not been performed.

IMPLEMENTATION ISSUES

Monitoring of patients in whom dialysis is delayed may be difficult if the resources are not available. Given the increasing shortage of nephrologists in the face of increasing numbers of patients with advanced kidney failure, new approaches are needed. One approach might be to use renal nurse practitioners and physician assistants, to closely follow patients in whom the decision to defer dialysis has been made. Protocols could be constructed to trigger referral for start of dialysis in such situations.

CLINICAL PRACTICE RECOMMENDATIONS FOR GUIDELINE 2: PERITONEAL DIALYSIS PRESCRIPTION TARGETS AND MEASUREMENTS

In a PD prescription, there are certain general considerations.

2.1 Regardless of delivered dose, if a patient is not thriving and has no other identifiable cause other than possible kidney failure, consideration should be given to increasing dialysis dose (see Table 11).

2.2 In a patient with minimal RKF, a continuous (rather than intermittent) 24 h/d of PD dwell PD prescription should be used to maximize middle-molecule clearance.

2.3 If either peritoneal Kt/V_{urea} is at least 1.7 or 24-hour urine output is less than 100 mL, monitoring of RKF is not required for monitoring the dose of PD. However, periodic measurement of RKF may be of value in this group of patients for the reasons noted in Table 12.

2.4 All measurements of peritoneal solute clearance should be obtained when the patient is clinically stable and at least 1 month after resolution of an episode of peritonitis.

2.5 More frequent measurements of either peritoneal urea clearance or RKF should be obtained when clinically indicated (see Table 13).

2.6 When calculating Kt/V_{urea}, one should estimate V from either the Watson or Hume equation in adults. In the absence of evidence, use of the patients' ideal or standard (rather than actual) weight should be considered in the calculation of V.

2.7 The determination of peritoneal C_{Cr} is of little added value for predicting risk for death; therefore, for simplicity, adequacy targets are based on urea kinetics only. Peritoneal creatinine excretion rate may be used to monitor estimates of muscle mass over time.

2.8 During the monthly evaluation of the PD patient, nutritional status should be estimated. Serum albumin levels should be monitored, and when obtaining 24-hour total solute clearances, estimations of dietary protein intake (DPI; such as nPNA) should be measured.

Table 11. Possible Indications To Consider Increasing the Dose of Dialysis

Uremic neuropathy
Uremic pericarditis
Nausea or vomiting otherwise unexplained
Sleep disturbance
Restless leg syndrome
Pruritus
Uncontrolled hyperphosphatemia
Evidence of volume overload
Hyperkalemia
Metabolic acidosis unresponsive to oral bicarbonate therapy
Anemia

Table 12. Possible Clinical Indications for Obtaining a 24-Hour RKF Collection

Small-solute clearance measurement
24-hour urine volume
24-hour urine sodium excretion
Creatinine generation rate

RATIONALE

Regardless of delivered dose, if a patient is not thriving and has no other identifiable cause other than possible kidney failure, consideration should be given to increasing the dialysis dose. There are many reasons that a dialysis patient fails to do well. Often, failure to do well on PD therapy relates more to comorbidity[174] or complications (such as peritonitis) than to adequacy. However, close examination of the 2 randomized trials of CAPD patients comparing small-molecule clearances gives some support to increasing dialysis in the symptomatic patient. In the ADEMEX Study, lower prescription (total average Kt/V_{urea} of 1.8 versus 2.27) resulted in more deaths from CHF (13.4% versus 5.7% in the intervention group; $P < 0.05$) and uremia, hyperkalemia, and/or acidosis (12.2% versus 5.1% in the intervention group; $P < 0.05$). More patients in this unblinded study were withdrawn because of uremia in the control group (5% versus none in the intervention group). Another randomized trial confirmed these results. Six percent of those in the group with total Kt/V_{urea} of 1.5 to 1.7 were withdrawn because of "inadequate" dialysis versus none in the groups with total Kt/V_{urea} of 1.7 to 2.0 and greater than 2.0 ($P = 0.002$ comparing all 3 groups). In addition, another 8% were withdrawn because of inadequate ultrafiltration in the group with Kt/V_{urea} of 1.5 to 1.7 versus 4% and 1% in the groups with total Kt/V_{urea} of 1.7 to 2.0 and greater than 2.0, respectively ($P = 0.012$). The group with the lowest clearance also required more erythropoietin. In the opinion of the Work Group, if a patient has symptoms possibly attributable to inadequate dialysis, such as anorexia, nausea, anemia, and hyperkalemia, or if volume overload is present, consideration should be given to increasing the dialysis dose.

Two additional indications listed in Table 11 for increasing the dialysis dose are uremic pericarditis and neuropathy. Tradition suggests that if a pericardial rub develops in a dialysis patient, the intensity of dialysis should be increased. This is an area that is poorly studied. Uremic neuropathy also is not very well understood, but if it develops, the dose of dialysis should be increased, with attention to removal of middle molecules.

There are no convincing data to support increasing small-molecule clearance to improve nutritional status or QOL. A study randomly assigned CAPD patients on 3

Table 13. Clinical Indications for Measurement of Peritoneal or Kidney Clearance

Routine monitoring of total solute clearance
Documentation of delivered total solute clearance after a prescription change
Patient who has failure to thrive
Patient who is hypertensive or volume-overloaded
During an occasional evaluation of any other unsuspected clinical problem

CAPD exchanges to continue on this prescription (n = 42) or to increase to 4 exchanges (n = 40). Peritoneal Kt/V_{urea} stayed constant at 1.56 in the 6-L group and increased from 1.59 to 1.92 in the 8-L group. Net ultrafiltration was better in the latter group, as was nPNA, which increased from 1.10 to 1.24 ($P = 0.05$), but there was no change in serum albumin level.[175] Another study increased the prescribed PD in 23 patients with a subsequent increase in peritoneal Kt/V_{urea} from 1.62 to 1.96, which was associated with an increase in serum albumin level from 3.55 to 3.83 g/dL.[176] It was unclear whether the increase in serum albumin level was caused by improved volume status (weight actually decreased and nPCR did not change). Others found that increasing the PD prescription to offset the loss of RKF did not result in an improvement in protein intake.[177] The NECOSAD reported that RKF correlated significantly with many parameters of the Kidney Disease-QOL (physical functioning, role limitations, social functioning, mental health, vitality, bodily pain, general health, symptoms, effect of kidney disease on daily life, sleep disorders, and overall health rating). Peritoneal clearances correlated with none of these.[44] In the ADEMEX Study, QOL was similar in the groups randomized to the higher small-molecule clearance relative to the lower target (total average Kt/V_{urea} of 1.8 versus 2.27).[40] In addition, patients with a serum albumin level less than 3 g/dL at the start had similar survival whether administered the higher or lower delivered dose. In confirmation of these results, patients randomized to a total Kt/V_{urea} of 1.5 to 1.7 had outcomes in respect to composite nutritional index and serum albumin level similar to patients with higher total Kt/V_{urea}.[39] In an observational study of anuric Chinese CAPD patients, serum albumin level did not correlate with Kt/V_{urea}.[67] Mean Kt/V_{urea} of these patients was 1.72 to 1.73 during the course of the 2-year observation. Serum albumin level in PD patients appears to be linked to inflammation and volume overload.[49,57,178,179]

In summary, if the patient appears to have uremic signs and symptoms, the PD prescription can be changed to increase small-molecule clearance. However, there are no convincing data that this will lead to better nutritional status, survival, or QOL.

In a patient with minimal RKF, continuous (rather than intermittent) (24 h/d of PD dwell) PD prescription should be used to maximize middle molecule clearance. Middle-molecule clearance, in contrast to small-molecule clearance, is much more a function of total time of dialysis rather than dialysate flow rate. Because evidence suggests that middle molecules, such as β-amyloid, contribute to joint and bone disease in the long term, it seems reasonable to maximize middle-molecule clearance in PD patients. β_2-Microglobulin levels increased over time in the CANUSA Study and were associated with increased risk for death and hospitalization.[65] Maximizing middle-molecule clearance is achieved best by performing continuous PD without dry periods. It is unclear whether starting PD with a "dry abdomen" as a form of incremental dialysis in patients with significant RKF has benefits (such as protection of the peritoneal membrane against continuous glucose exposure or potential enhancement of peritoneal immune function). Further research is needed in this area.

If either peritoneal Kt/V_{urea} is at least 1.7 or 24-hour urine output is less than 100 mL, monitoring RKF is not required for monitoring dose of PD. However, periodic measurement of RKF may be of value in this group of patients for the reasons noted in Table 12. A study of anuric patients on APD therapy with a 24-hour prescription[71] found that predictors of survival were age; SGA score of C, indicating malnutrition (RR, 6.97; $P = 0.006$); and diabetes, but not time-averaged total C_{Cr}. Anuria was carefully defined in this study as 24-hour urine volume less than 100 mL and GFR (determined by using the average of urea and creatinine kidney clearance based on 24-hour collection of urine) less than 1 mL/min/1.73 m^2. Patients with any RKF continued to provide 24-hour urine collections; they had an average kidney clearance of 1.92 L/wk/1.73 m^2 at the start of the study and 0.59 L/wk/1.73 m^2 at 24 months. In this study, peritoneal clearances were repeated every 2 months until the planned targets were reached, and then every 6 months.

Similarly, in the ADEMEX Study, patients brought in repeated clearances (urine and peritoneal) every 2 months until the target was achieved; then the frequency was reduced to every 4 months.[38] In the Hong Kong randomized trial, after initial adjustment of the prescription to get the patient into the target total Kt/V_{urea} range (which, in some cases, required reducing the peritoneal dose), the clearance (kidney and peritoneal) was repeated in 4 to 6 weeks, then every 6 months until the study ended (15 months after the last patient recruitment).[39] Average kidney Kt/V_{urea} decreased steadily over time and was less than 0.1 by the study end point in all 3 groups. The CAPD prescription was continuously adjusted upward to enable patients to stay within the total Kt/V_{urea} targets of 1.5 to 1.7, 1.5 to 2.0, and greater than 2.0.

In an observational study, urine volume was determined every 2 months at clinic visits by having the patient measure daily urine volume for the 7 days before the visit; this was normalized to 1.73 m^2.[48] Actual measurement of kidney and peritoneal clearance was performed every 6 to 12 months. Total fluid removal (ultrafiltration plus urine volume) was a strong predictor of survival (RR, 0.90 for every 100 mL/24 h; $P < 0.01$). RKF also was a strong predictor of survival (RR, 0.41 for every increase in RKF of 1 mL/min/1.73 m^2; $P < 0.01$).

Because a total Kt/V_{urea} greater than 1.7 has not been associated with clinical benefits, if this goal is achieved through PD, there would seem to be no need for measuring RKF. However, given the importance of RKF for survival, measuring 24-hour urine volume may focus attention on remaining kidney function. Furthermore, in the opinion of the Work Group, for patients who have persistent edema, measuring sodium losses in urine and effluent may help in management. However, there are few data for this.

There is considerable heterogeneity in the decrease in RKF in PD patients.[89] Therefore, measurement of RKF seems warranted to monitor this important predictor of outcome.[89,101] Peritonitis may have a negative impact on RKF; therefore, reassessing RKF after an episode of peritonitis would appear reasonable.

All measurements of peritoneal solute clearance should be obtained when the patient is clinically stable and at least 1 month after resolution of an

episode of peritonitis. Peritonitis transiently changes the patient to a high transporter and decreases ultrafiltration per dextrose concentration used. Therefore, a dialysate clearance obtained close to an episode of peritonitis may either overestimate (because of the high transport status) or underestimate (because of the decrease in convection from decreased ultrafiltration) clearance of small molecules. Therefore, it appears best to defer a collection until 1 month or more after peritonitis. A change in prescription may require time for the patient to reach equilibrium; therefore, a delay in performing the collection is warranted.

More frequent measurements of either peritoneal urea clearance or RKF should be obtained when clinically indicated (see Table 13). For a patient with failure to thrive with no alternative explanation, repeated clearance of urine and peritoneal effluent may determine whether uremia is contributing to the problem. With the development of intravascular volume depletion, inadvertent use of NSAIDs, or other intercurrent events, a PD patient may lose significant RKF such that the PD prescription is no longer adequate. A decrease in dialysate dextrose concentration may result in decreased ultrafiltration and decreased clearance, leading to uremia. Overzealous blood pressure control also may lead to loss of RKF. Last, the patient may change the timing of the exchanges (ie, shortening some and lengthening others excessively), leading to inadequate dialysis. Repeating the clearance, if clinically indicated, may uncover these potential problems. Consideration should always be given to nonadherence with the prescription if the patient is not doing well. Nonadherence may be investigated by assessing the supplies ordered, as well as home supply inventory and analysis of the cycler memory system (if available).

When calculating Kt/V_{urea}, one should estimate V from either the Watson or Hume equation in adults. In the absence of evidence, use of the patient's ideal or standard (rather than actual) weight should be considered in the calculation of V. For the patient close to or at dry weight, the Watson or Hume equation is acceptable.[180,181] The Watson equations tend to underestimate total body weight.[182,183] In underweight patients, it also seems sensible to adjust the clearance for ideal body weight. An international cross-sectional study[184] examined the nutritional status of 224 CAPD patients, of whom 71 were anuric, defined as no urine output. When parameters of severely malnourished patients were adjusted to desired weight, nPCR was decreased (0.76 versus 0.98 for well-nourished patients), as was Kt/V_{urea} (1.40 versus 1.68). These results suggest it is important to normalize V to calculate Kt/V_{urea} in malnourished patients. In amputees, total body water (TBW) must be calculated by determining the percentage of body weight lost in the amputation (using a nomogram) and dividing actual weight by percentage of body composition remaining, applying this weight with the nonamputated height to the Watson formula to determine the proportion of body water. This proportion then is multiplied by actual weight to obtain V.[185]

However, the correct determination of V for overweight patients is unclear.[186] The Watson formula overestimates TBW in obese patients and underestimates it in overhy-

drated patients.[183] Body size does not affect dialysate to plasma (D/P) ratio of small solutes.[187]

Determination of peritoneal C_{Cr} is of little added value for predicting risk for death; therefore, for simplicity, adequacy targets are based on urea kinetics only. Peritoneal C_{Cr} may be used to monitor estimates of muscle mass over time. Total C_{Cr} in patients with RKF is much a reflection of RKF. In the absence of RKF, C_{Cr} seems to add little to the use of urea clearance. A study examined 912 PD patients by using the USRDS data set, as well as by questionnaires completed by centers, and found that kidney urea clearance (but not dialysate urea clearance) was predictive of 12-month mortality. Neither kidney nor dialysate C_{Cr} were predictive.[43] However, peritoneal and kidney creatinine excretion is a good measure of muscle mass and may be used to measure this sequentially if it seems appropriate.[188,189]

During the monthly evaluation of the PD patient, nutritional status should be estimated. Serum albumin levels should be monitored and when obtaining 24-hour total solute clearances, estimations of DPI (such as nPNA) should be measured. Nausea, vomiting, and appetite suppression are acknowledged symptoms of uremia. Uremic patients tend to have decreased DPI,[190] and spontaneous DPI decreases as renal rGFR decreases to less than 50 to 25 mL/min.[191] These tendencies may be exacerbated during the period before the initiation of dialysis therapy when many patients are not only anorexic, but also are acidotic and often treated with low-protein "renal protective" diets. As a result, patients may show signs of protein malnutrition when they present for dialysis. Dialysis itself is associated with unique metabolic and nutritional problems. PD patients may have a decreased appetite and early satiety[192,193] and typically lose 5 to 15 g of protein and 2 to 4 g of amino acids per day in their dialysate.[194] These losses amount to a net loss equivalent to 0.2 g protein/kg/d and tend to be higher in rapid transporters than low transporters. These losses are increased transiently during episodes of peritonitis,[195] at times doubling after even a mild episode. Studies of patients with CKD stage 5[196–199] showed that some of the most important predictors of patient risk for death are such surrogates of nutritional status as serum albumin level, SGA score, and DPI estimate. Hence, it would be appropriate to monitor and maintain normal nutritional status in patients on PD therapy. However, it is important to note that there have been no prospective randomized trials that evaluated a patient's RR for death when 2 different levels of a surrogate for nutritional status were compared as the target intervention.

A patient's RR for death correlates with surrogates of nutritional status. It is well recognized that such markers of "nutritional status" as serum albumin level, estimation of DPI, and SGA score[200] are influenced by many additional clinical parameters other than nutrition-related ones; therefore, they must be treated as imperfect surrogates for nutritional status of a patient. For example, in an individual PD patient, the significance of an isolated serum albumin level must be viewed with caution. An isolated level does not necessarily predict nutritional status. Levels must be followed up over time and interpreted

in the context of other patient-related issues, such as peritoneal membrane transport type, total solute clearance, volume status, presence of chronic liver disease, presence of comorbid diseases, and any inflammatory state.

Most (95%) nitrogen intake in humans is in the form of protein. Therefore, when the patient is in a steady state (not catabolic or anabolic), total nitrogen excretion multiplied by 6.25 (there are ~6.25 g protein per gram of nitrogen) is thought to be an estimation of DPI.[201] Estimated DPI is calculated from urea nitrogen appearance in dialysate and urine. Multiple equations have been derived, some of which have been validated in CAPD (but not nightly intermittent PD [NIPD]) patients (protein equivalent of total nitrogen appearance [PNA] = protein catabolic rate [PCR] + protein losses). These estimations initially were called the PCR. However, PCR actually represents the amount of protein catabolism exceeding synthesis required to generate an amount of nitrogen that is excreted, ie, PCR is a net catabolic equivalent. Thus, because these calculations are based on nitrogen appearance, the term is more appropriately called the protein equivalent of nitrogen appearance, or PNA. Following up a patient's nPNA (discussed next) over time is a way to estimate DPI over time to ensure adequate nutritional status. A baseline PNA should be obtained during training. These should be recalculated every 4 to 6 months by using the same 24-hour dialysate and urine collections used to monitor solute clearances. One cause of a decreasing nPNA would be decreasing DPI at times because of suboptimal total solute clearance.

For comparison purposes, it is recommended that PNA be normalized for patient size (ie, nPNA). What patient weight (actual, standard, ideal) to use for that normalization is controversial. Depending on the weight used in calculating nPNA, there may or may not be a statistical relationship between clinical evidence of malnutrition and nPNA values less than target. PNA normalized by actual weight tends to be high or may appear to be increasing over time in malnourished individuals if normalized (divided) by a progressively smaller malnourished weight compared with the patient's baseline weight.[202] It therefore is the opinion of the Work Group that ideal weight be used for the normalization process.

Data from the Centers for Medicare and Medicaid Services (CMS) Clinical Performance Measures (CPM) Project for the year 2000 found that, in long-term FPD patients, mean nPNA was 0.95 ± 0.31 g/kg/d, normalized creatinine appearance rate was 17 ± 6.5 mg/kg/d, and mean percentage of lean body mass was 64% ± 17% of actual body weight.[203]

There is some controversy about what amount of DPI, in terms of grams of protein per kilogram of body weight, is needed to maintain a positive nitrogen balance in PD patients. Early studies suggested that DPI of at least 1.2 g/kg/d was needed to maintain nitrogen balance,[204,205] a value considerably higher than that recommended for healthy individuals. The NKF KDOQI guidelines recently recommended DPI for long-term PD patients of 1.2 to 1.3 g/kg/d.[35] Two cross-sectional studies suggested that patients who show no signs of malnutrition seem to eat less protein (0.99[206] and 0.88[207] g/kg/d, respectively). Results likely are caused by variations in the patient populations studied, historical dietary patterns, and amounts of RKF present. Therefore, several investigators

proposed that daily protein intake in these patients should be in the range of 0.9 to 1.1 g/kg/d.[208,209] If values are less than this amount, one should consider looking for potential causes of decreased DPI, such as intentional low DPI, gastroparesis, comorbidity, chronic inflammation, and suboptimal small-solute removal.

There is little evidence from prospective RCTs that increasing small-solute removal results in an improvement in surrogate markers for nutritional status. In both the ADEMEX Study and Hong Kong trials, the intervention groups (higher small-solute clearance) did not have an improvement in surrogate measurements of nutritional status (albumin level and PNA). If surrogate markers for nutritional status suggest that the patient's nutritional state is declining, one should consider evaluation for new comorbidity, additional dietary evaluation, dietary supplements, and, if no other cause is identified, an increase in dialysis dose.

LIMITATIONS

There is a marked lack of high-quality studies of PD patients examining different doses of PD. Only 2 randomized trials have been performed, both in CAPD patients. There are no randomized trials of different doses of small-molecule clearances in APD patients. There also are no studies comparing initiation of PD therapy with a cycler at night and a dry day versus CCPD. There are no randomized trials targeting different levels of blood pressure control. There are only 2 randomized trials of interventions to protect RKF and none examining the effect of different prescriptions (especially APD versus CAPD) on RKF. Control of middle molecules is believed to be important to prevent long-term complications, but studies of this are mostly lacking.

IMPLEMENTATION ISSUES

Obtaining a clearance in PD patients is very dependent on the cooperation of the patient. The patient must bring the used dialysate to the dialysis unit. This may be difficult for elderly or weak patients unable to lift heavy objects or those with limited transportation. If the patient is told to sample the effluent and record the weight (for CAPD) or drain volume (for APD), the center is dependent on the patient providing the correct numbers. Furthermore, on the day of the clearance, the patient is more likely to do the proper full prescription. Therefore, the measurement, at best, is that of that particular day's dialysis and not necessarily reflective of average clearance. To some extent, use of a cycler with a mechanism of monitoring the use of the cycler and time on the cycler could be used.[210] This cycler is not universally available and increases the cost of treatment.

CLINICAL PRACTICE RECOMMENDATIONS 3: RECOMMENDED LABORATORY MEASUREMENTS FOR PERITONEAL MEMBRANE FUNCTION AND ULTRAFILTRATION VOLUME

Total solute clearance and peritoneal effluent volume ultimately are influenced by peritoneal membrane transport characteristics. Multiple tests are documented to be efficacious for determining peritoneal membrane transport. None of these tests has been shown to be clinically superior to the others (see Table 14).

- **3.1 Each center should choose one of these tests to use when characterizing peritoneal transport in their patients.**
- **3.2 Baseline peritoneal membrane transport characteristics should be established after initiating a daily PD therapy.**
- **3.3 Data suggest that it would be best to wait 4 to 8 weeks after starting dialysis to obtain this baseline measurement.**
- **3.4 Peritoneal membrane transport testing should be repeated when clinically indicated (see Table 15).**
- **3.5 All measurements of peritoneal transport characteristics should be obtained when the patient is clinically stable and at least 1 month after resolution of an episode of peritonitis.**

BACKGROUND

After PD therapy is initiated, total solute removal is related to residual kidney and peritoneal effluent volumes and the concentration of the solute in question in each of those volumes. The background for, definitions of, and frequency of how and what to measure to determine total solute removal or clearance are outlined in CPG 2 and CPR 2. During a typical PD dwell, peritoneal effluent drain volume and concentration of solutes in that drain volume will vary from patient to patient and are dependent on the individual patient's peritoneal membrane transport characteristics, infused volume/exchange, concentration and type of osmotic agent used, rates of lymphatic absorption of fluid, and dwell time/exchange.[211] Although in our goal to replace lost RKF, we have been focused on the movement of solutes and fluid from blood to the peritoneal cavity (and ultimately, by draining the peritoneal fluid, removal from the body), it is important to note that solutes (ie, osmotic agents) and fluid also potentially are absorbed from the peritoneal cavity. To most efficiently optimize solute and fluid removal in each patient, one must know and understand each individual's peritoneal membrane transport characteristics and recognize that there is potential that they may change over time.[212,213]

RATIONALE

Definitions

Two of the typical laboratory measurements routinely obtained in PD patients are: (1) those used to quantify and document amount of solute removed from the body (such as the weekly Kt/V_{urea} or C_{Cr} described previously), and (2) tests that classify peritoneal membrane transport characteristics (described next). Tests that measure

Table 14. Standardized Tests for Evaluating Peritoneal Membrane Transport/Function

Aspect of Peritoneal Function	Method of Peritoneal Function Testing		
	PET	SPA	PDC
Small solute transport	D/P* creatinine	MTAC creatinine	Area permeability
Ultrafiltration capacity	Drain volume	Drain volume	Estimates ultrafiltration coefficient
Ultrafiltration via water channels	D/P Na	Model for Na channel	—
Fluid absorption	—	Dextran 70	Derived
Peritoneal blood flow	—	—	—
Permeability to macromolecules	—	Restriction coefficients	Large-pore flow

Abbreviations: SPA, standard peritoneal permeability analysis; MTAC, mass transfer area coefficient.
* Ratio of concentration of solutes in dialysate (D) to plasma (P).

peritoneal membrane transport characteristics are designed to define or classify an individual patient's rate of solute diffusion and potential fluid removal, not quantify actual amount of solute or volume of fluid removed. After an individual patient's peritoneal membrane transport characteristics are defined, one can use such data to guide prescription management and predict what the delivered solute removal may be with a certain prescription. As noted, it is recommended that dialysate and urine be collected and solute removal be measured to accurately quantify a patient's delivered dose of dialysis.

Each center should choose one of these tests to use when characterizing peritoneal transport in their patients. It is known that peritoneal membrane transport characteristics vary from patient to patient. To optimize solute removal and ultrafiltration volumes, it is helpful to know each patient's individual peritoneal membrane transport properties. Multiple tests have been developed to evaluate various aspects of peritoneal membrane function (see Table 14). There have been no prospective randomized trials designed to determine which test is best for prescription management. Each test has its strengths and weaknesses, and all are useful. These have been reviewed recently.[214]

Traditionally, peritoneal membrane transport/function has been assessed by using the standard PET.[211] The PET has been standardized both procedurally and interpretably to classify peritoneal membrane function. It was designed and initially used primarily to evaluate small-solute transport characteristics, and although ultrafiltration properties of the peritoneal membrane are linked, the original PET was not designed to differentiate all the variations in peritoneal membrane transport/function that result in pathological alterations in ultrafiltration capacity.

A modification of the original PET using 1.36%/1.5% dextrose/dextran 70, called the standard peritoneal permeability analysis (SPA), was developed to better evaluate mass

Table 15. Clinical Indications for Repeat Peritoneal Membrane Transport Testing

Presence of unexplained volume overload
Decreasing drain volume (DV) on: overnight dwell (CAPD), or daytime dwell (APD)
Increasing clinical need for hypertonic dialysate dwells to maintain DV
Worsening of hypertension
Change in measured peritoneal solute removal (K/V_{urea})
Unexplained signs or symptoms of uremia

Abbreviations: CAPD, continuous ambulatory peritoneal dialysis; APD, automated peritoneal dialysis

transfer area coefficients (MTAC) of small- and middle-molecular-weight solutes and also better determine residual volume and ultrafiltration kinetics.[215] The 1.36%/1.5% dextrose/dextran 70 solutions were chosen so there would be less of an osmotic gradient for ultrafiltration and therefore one would be able to better determine the true diffusive MTAC characteristics of the membrane in a situation in which there would be less ultrafiltration and its associated convective removal of solutes.

The standard PET subsequently was modified, and 3.86%/4.25% dextrose solutions were substituted to maximize crystalloid osmotic ultrafiltration and optimize the ability to evaluate pathological variations in ultrafiltration capacity.[216] This modification allows one to evaluate aquaporin-mediated water transport and the sodium- versus water-removal characteristics of peritoneal transport. The PET and SPA use single dwells and direct measurements to characterize peritoneal transport properties.

Another procedure, the PDC test, uses data from multiple dwells (typically 5) performed during a 24-hour period.[217] Data are combined in a mathematical model to estimate peritoneal transport characteristics. In addition to establishing MTAC, the PDC test is better able to determine peritoneal fluid absorption rates and macromolecule permeability.

There are geographic variations in the use of tests for classifying peritoneal membrane function. The PET is the simplest procedure to perform and, as expected, has the most clinical experience related to its use. There are no data to suggest that one test is better than another in common clinical settings; hence, each center should use the test they are most comfortable with. The International Society for PD has recommended that a modified PET (3.86%/4.25% dextrose) dwell be used to optimally evaluate patients with ultrafiltration failure.[218]

Baseline peritoneal membrane transport characteristics should be established after initiating a daily PD therapy. It is recognized that to optimize solute removal and ultrafiltration volumes, one must understand peritoneal physiological processes and know each patient's individual peritoneal membrane transport characteristics. This could be done by careful observations of such clinical parameters as blood pressure, volume status, physical examination findings, well-being, and serum chemistry test results, adjusting the peritoneal prescription as indicated. One is likely to be better able to do this if one documents peritoneal membrane transport characteristics in each patient. Once established, these data can be used to guide prescription writing and predict clearances and ultrafiltration volumes. Kinetic modeling programs have been developed that use peritoneal membrane transport test data from the standard PET to help in prescription management. These have been validated for clinical use.

Data suggest that it would be best to wait 4 to 8 weeks after starting dialysis therapy to obtain this baseline measurement. The initial instillation of dialysate into the peritoneal cavity and the initiation of PD therapy is associated with mild changes in local cytokine production, peritoneal vascularity, and blood flow. These changes in peritoneal anatomy and perfusion potentially can influence peritoneal membrane transport. Historical data have suggested there is a small increase in D/P ratio for small solutes

during the first month on PD therapy.[219] This phenomenon recently was confirmed in a longitudinal analysis of 50 new PD patients.[220] One-week, 1-month, and 1-year PET results from individual patients were compared. Significant changes in D/P urea (0.91 versus 0.94), D/P creatinine (0.55 versus 0.66), and end dialysate dextrose concentration over initial dialysate dextrose concentration (D/D_0) glucose (0.38 versus 0.36) were noted. One-month PET results correlated better with 1-year results than did 1-week PET results. D/D_0 values for glucose changed the least during the first month, and 1-week D/D_0 values better predicted transport characteristics than 1-week drain value.

Based on these and historic data, it is recommended that the "baseline" peritoneal membrane transport study is obtained after the first 4 to 8 weeks of starting dialysis. During training, one could "estimate" peritoneal membrane transport rate by measuring the drain volume from a 4-hour dwell of 2.5% dextrose and comparing expected D/P ratios of creatinine to the patient's observed drain volume. However, as noted, the observed drain volume is not as predictive as other laboratory measurements. For most patients at the initiation of dialysis therapy, there is some RKF present. Therefore, estimating delivered clearance and ultrafiltration volumes from D/P ratio predicted by drain volumes observed during training suffice until a formal PET and 24-hour dialysate collection can be obtained. Standard clinical practice usually involves a timed 4-hour dwell with 2.5% dextrose during training and a follow-up PET at about 1 month after initiating PD therapy, at which time other issues regarding prescription management can be reviewed.

Peritoneal membrane transport testing should be repeated when clinically indicated (see Table 15). In general, peritoneal transport is stable over time. However, small cohort studies that evaluated peritoneal transport characteristics over time, often with a short follow-up period, suggest that in some patients, peritoneal transport changes.[221] Impaired ultrafiltration is the most frequent clinically noted abnormality. The prevalence of this change is dependent on dialysis vintage. One review using a clinical definition for ultrafiltration failure (defined as a need for hypertonic exchanges) suggested it was present in 3% of patients at 1 year and 31% after 6 years.[222] In another cross-sectional study of patients on PD therapy for a median of 19 months (range, 0.3 to 178 months) and using a laboratory definition of ultrafiltration failure (ultrafiltration $<$400 mL after a 4-hour dwell with 4.25% dextrose), impaired ultrafiltration was noted in 23% of patients.[216] It appears (from these studies in unselected patients) that over time, there tends to be an increase in transport manifested by higher MTACs, higher D/P ratios for small solutes, decrease in ultrafiltration when using glucose-containing fluids, and increased restriction to the transport of macromolecules.[223] These clinical observations suggest there tends to be an increase in number of microvessels per unit of peritoneal surface area, along with decreased permeability to large-molecular-weight solutes. The net result is that the diffusive rate of solute transport tends to increase and drain volume/dwell tends to decrease. However, in many patients, total solute removal/dwell often remains stable because of these two offsetting phenomena.

As a result of the observed stability of peritoneal transport over time in most patients, one does not need to routinely document individual patients' peritoneal membrane

transport characteristics over time with routine laboratory measurement (peritoneal membrane transport testing). However, one needs to clinically assess drain volume and clinical volume status in each patient on a regular basis. Drain volume can be assessed during a clinical visit by reviewing a patient's overnight (for CAPD) or daytime (for APD) drain volume and assessing the patient's need to use hypertonic dialysate solutions to maintain euvolemia. If one suspects a change in clinical status, peritoneal membrane testing should be repeated (see Table 15).

As noted, kinetic modeling programs have been developed that use peritoneal membrane transport test data from the standard PET to help in prescription management, and they have been validated for clinical use. As a result, most centers use the standardized PET as the baseline test to characterize peritoneal membrane transport. However, it now is recommended that one use a 3.86%/4.25% dextrose PET to work up a patient suspected to have ultrafiltration failure.[218] Part of that evaluation includes comparison of current D/P data to historical baseline data. The 2.27%/2.5% dextrose PET and 3.86%/4.25% dextrose PET were compared, and no clinical differences between D/P ratios for such small solutes as creatinine were found.[224] Two studies compared 2.27%/2.5% dextrose with 3.86%/4.25% dextrose PET. Forty stable PD patients were found to have little difference in D/P creatinine values, but expected differences in ultrafiltration profile.[225] A subsequent study of 154 patients compared the 2 tests, found little clinical differences in D/P creatinine values, and established reference values for the 4.25% dextrose PET.[226]

These data suggest that in common clinical practice, one could compare D/P ratios for small-solute transport between tests. If ultrafiltration failure is suspected, the 3.86%/4.25% dextrose PET would be most useful, even if a 2.27%/2.5% PET was done at baseline.

All measurements of peritoneal transport characteristics should be obtained when the patient is clinically stable and at least 1 month after resolution of an episode of peritonitis. Peritonitis is associated with peritoneal inflammation, which, in turn, is associated with hyperemia and changes in peritoneal transport. These changes usually are transient. The most striking clinical finding noted during an episode of peritonitis is impaired ultrafiltration.[227] This is associated with an increase in peritoneal transport of low-molecular-weight solutes and increased rates of glucose absorption. These changes usually are transient and typically resolve within a month after resolution of the peritonitis.[228,229]

LIMITATIONS

There have been no prospective randomized trials comparing patient outcomes with the use of various test methods. Therefore, one cannot be recommended over the other. However, it is unlikely there will be differences among test methods, and that study has not been recommended. These tests are designed to classify and evaluate membrane function. Although suggested by the literature that peritoneal transport type may influence patient outcome, it is controversial about whether patients with different baseline transport characteristics have different clinical outcomes or need to be on different types of PD therapies. Patients with all types of peritoneal function have been managed

successfully on each of the different types of PD modalities (CAPD versus APD). The number of patients with ultrafiltration failure at any one center is limited, and data are just emerging on identifying them with use of 3.86%/4.25% dextrose PET. Therefore clinical data for outcomes after adjusting therapy based on PET findings and the use of newer PD fluids are lacking. With current therapies/solutions, it was shown that longitudinal laboratory monitoring of peritoneal transport of individual patients is not indicated. It is possible that if routine testing is no longer done as newer solutions are used, one may not have the data to evaluate longitudinal changes in transport and response to therapy with the use of these solutions.

IMPLEMENTATION

Most centers are already using standard PET in clinical practice. Many are routinely monitoring transport changes over time (most on a yearly basis, although the prior KDOQI PD Adequacy Guidelines recommended more frequent monitoring). These CPRs are less demanding than the original KDOQI PD Adequacy Guidelines and—as CPRs instead of CPGs—should make implementation easier because there will be no related performance measures.

COMPARISON TO OTHER GUIDELINES

The frequency of testing has been decreased compared with prior KDOQI PD Adequacy Guidelines. They are similar to anticipated revisions of the Canadian and European guidelines for PD.

CLINICAL PRACTICE RECOMMENDATIONS 4: WRITING THE PERITONEAL DIALYSIS PRESCRIPTION

The PD modality has an impact on adherence and QOL, which are important considerations in writing a PD prescription. Ultrafiltration, which is important in optimizing volume control and thus patient survival, is dependent on the prescription and peritoneal membrane characteristics. Clearance of middle molecules, while not proved to influence patient survival, should be an important consideration in the prescription.

4.1 The patient's schedule and QOL should be taken into account when prescribing PD.

4.2 To optimize middle-molecule clearance in patients who have minimal RKF, the PD prescription should preferentially include dwells for the majority of the 24-hour day. This is recommended even if small-molecule clearance is above target without the longer dwell.

4.3 As tolerated by the patient, to optimize small-solute clearance and minimize cost, one should first increase instilled volume per exchange before increasing the number of exchanges per day. The exchange volume of the supine exchange(s) should be increased first because this position has the lowest intra-abdominal pressure.

4.4 The patient's record of PD effluent volume should be reviewed monthly, with particular attention to the drain volume from the overnight dwell(s) of CAPD and the daytime dwell(s) of APD.

4.5 A number of techniques can be used to optimize volume and blood pressure control.

4.5.1 To achieve the desired volume status, the lowest possible dialysate dextrose concentration should be used.

4.5.2 When appropriate, implement dietary sodium and fluid restriction.

4.5.3 In patients with RKF, to achieve dry weight, diuretics may be preferred to increasing dialysate dextrose concentration.

4.5.4 Drain volume should be optimized during the overnight dwell(s) of CAPD and the daytime dwell(s) of APD to maximize solute clearance and ultrafiltration volume.

4.5.5 In patients who are hypertensive or who show evidence of volume overload, ultrafiltration generally should not be negative (ie, no absorption) for any daytime or nighttime exchanges.

BACKGROUND

As explained in CPGs 2 and 4, the PD prescription requires frequent review to ensure that clearance- and volume status–related guidelines are being implemented. In determining the PD prescription, the required clearances and the effect on volume status are paramount, but other factors that need to be considered are potential effects on middle-molecule clearance and on QOL of patients and their caregivers.

RATIONALE

The patient's schedule and QOL should be taken into account when prescribing PD. The PD prescription can be onerous for patients and their caregivers. There is evidence that nonadherence is common and that it is more likely to occur with more demanding prescriptions, such as CAPD with 5 exchanges daily.[61] Some patients find larger dwell volumes difficult to tolerate.[38] Social factors and "burnout" are recognized as common problems in PD therapy and as causes of technique failure.[128] Accordingly, prescriptions should take the personal and social circumstances of patients into account. The implications of additional dwells, increased dwell volumes in CAPD and APD, and longer cycler times in APD should be discussed with patients and/or their caregivers with a view to designing a prescription that can meet both medical and social requirements and maintain reasonable QOL.

To optimize middle-molecule clearance in patients who have minimal RKF, the PD prescription should preferentially include dwells for the majority of the 24-hour day. This is recommended even if small-molecule clearance is above target without the longer dwell. The term "middle molecule" refers to molecules of molecular weight greater than 1,000 kd. There has long been controversy concerning their importance in uremic toxicity in patients with kidney failure generally and in both HD and PD patients. To date, no high-level clinical study has provided conclusive evidence that middle-molecule clearance determines important clinical outcomes in dialysis patients, although there is some weak, but suggestive, evidence for HD patients from the HEMO Study.[91] In PD patients, middle-molecule clearance is time dependent and not significantly influenced by dialysate flow rates or dwell volumes.[230] Prescriptions, such as standard CAPD or APD with full-duration day dwells, maximize middle-molecule clearance, and this is thought by some to be an advantage of PD over conventional intermittent HD. However, with the increase in popularity of APD in the past decade, there has been widespread use of prescriptions with short dwells or no day dwells at all, particularly in patients with RKF. Such prescriptions may facilitate fluid removal or improve patient QOL in that many APD patients tend to prefer not to carry peritoneal fluid in the daytime. However, there is concern that the dry day may compromise middle-molecule clearance and thus may be harmful to patients.

Such prescriptions often are used in patients with substantial RKF because Kt/V_{urea} targets can still be achieved easily. In such circumstances, middle-molecule clearance need not be a concern because RKF is a far more substantial contributor to middle-molecule clearance than any PD prescription. If such prescriptions are associated with low Kt/V_{urea} values, they need to be altered anyway, in accordance with CPG 2.1. The concern about middle-molecule clearance only arises in patients with minimal residual function and a dry day APD prescription that still meets Kt/V_{urea} targets. This may occur because the patient is small in body size or is a high transporter. In this situation, the disparity between adequate small-solute clearance and low middle-molecule clearance leads to concern. There is no evidence in the PD literature to guide prescriptions in this situation, but in the interests of patient safety, it is recommended that at least low-volume

long-duration dwells be prescribed. Given the lack of high-level evidence to support this statement, implementation should be tempered by QOL considerations for the patient and by the risk for mechanical complications, both of which may be affected negatively by long day dwells.

As tolerated by the patient, to optimize small-solute clearance in CAPD and minimize cost, one should first increase instilled volume per exchange before increasing the number of exchanges per day. The exchange volume of the supine exchange(s) should be increased first because this position has the lowest intra-abdominal pressure. In CAPD, the principal methods to increase peritoneal clearance are to either increase dwell volumes, typically from 2 to 2.5 L to 3 L, or increase frequency of exchanges, typically from 4 to 5 daily.[212] Both strategies are similarly effective in increasing peritoneal Kt/V_{urea}, and increased frequency of exchanges may have a greater benefit in enhancing ultrafiltration. However, increasing the dwell volume generally is preferred unless there are mechanical contraindications. This is because adherence to CAPD prescriptions with 5 daily exchanges has been shown to be particularly poor and may be associated with worse QOL. Also, the cost of increasing exchange frequency is greater than the cost of increasing dwell volumes. However, ultimately, patient preferences should be a major determinant of which strategy is followed.

If patients have concerns about tolerating increased dwell volumes in either CAPD or APD, consideration should be given to increasing nighttime dwell volumes initially. The rationale for this strategy is that increases in intraperitoneal pressure (IPP) are less for a given dwell volume in the supine or recumbent position compared with either sitting or standing.

The patient's record of PD effluent volume should be reviewed monthly, with particular attention to the drain volume from the overnight dwell(s) of CAPD and daytime dwell(s) of APD (see CPR 4.2).

A number of techniques can be used to optimize volume and blood pressure control (see CPRs 4.5.1 to 4.5.5).

LIMITATIONS

None of these individual prescription strategies have been shown to produce superior outcomes in RCTs. However, their effects on clearance and fluid removal are well recognized from clinical studies and clinical experience and are not controversial. The relative merits of particular strategies in a given patient need to take into account multiple personal and social factors that will vary among patients. These are not easily studied in clinical trials. In such situations, different strategies may need to be tried in a given patient until an optimal compromise among clearance, ultrafiltration, and QOL requirewments is achieved.

With regard to the middle-molecule recommendation, there is too little evidence to offer a firm guideline, but, just as when dealing with small-solute clearances, the best principle is to give the patient the benefit of the doubt and not provide lower clearances than have been shown to be safe by clinical studies. However, given the lack of evidence,

weight also should be given to other factors, such as QOL and risk for mechanical complications.

IMPLEMENTATION

Implementation of these recommendations requires only that patients be carefully evaluated monthly. At the evaluations, ultrafiltration and clearance requirements should be reviewed, with particular attention to how the prescription is affecting QOL and whether the patient is adherent to it. Appropriate changes could then be made.

6.1 Dialysis initiation:

6.1.1 Dialysis initiation should be *considered* for the pediatric patient when GFR is 9 to 14 mL/min/1.73 m^2 BSA and should be *recommended* when GFR is 8 mL/min/1.73 m^2 or less. GFR can be estimated by either averaging the measured creatinine and urea clearances by using a timed urine collection, using the Schwartz formula, or using a timed urine collection to determine C_{Cr} after a dose of cimetidine. Dialysis therapy initiation should be considered at the greater estimated GFR levels when the patient's clinical course is complicated by the presence of malnutrition, fluid overload, hypertension, hyperkalemia, hyperphosphatemia, acidosis, growth failure/decreasing height velocity, or neurological consequences of uremia. Before dialysis is undertaken, these conditions should be shown to be persistent and refractory to medication and/or dietary management.

6.2 Modality selection:

6.2.1 The decision regarding the selection of PD as a dialysis modality for the pediatric patient should take a variety of factors into account, including patient/family choice, patient size, medical comorbidities, and family support.

6.3 Solute clearance targets and measurements:

6.3.1 In the absence of definitive data correlating solute removal and clinical outcome in children, current recommendations for solute clearance in pediatric patients receiving PD are as follows:

6.3.1.1 The pediatric patient's clinical status should be reviewed at least monthly, and delivery of the prescribed solute clearance should render the patient free of signs and symptoms of uremia.

6.3.1.2 All measurements of peritoneal solute clearance should be obtained when the patient is clinically stable and at least 1 month after resolution of an episode of peritonitis.

6.3.1.3 More frequent measurements of peritoneal solute clearance and RKF should be considered when clinical events are likely to have resulted in decreased clearance or when new/worsening signs or symptoms of uremia develop.

6.3.1.4 Regardless of the delivered dose of dialysis, if a patient is not doing well and has no other identifiable cause other than kidney failure, a trial of increased dialysis is indicated.

6.3.2 For patients with RKF (defined as urine $Kt/V_{urea} > 0.1$/wk):

6.3.2.1 The minimal "delivered" dose of total (peritoneal and kidney) small-solute clearance should be a Kt/V_{urea} of at least 1.8/wk.

6.3.2.2 Total solute clearance should be measured within the first month after initiating dialysis and *at least* once every 6 months thereafter.

6.3.2.3 If the patient has RKF and residual kidney clearance is being considered as part of the patient's total weekly solute clearance goal, a 24-hour urine collection for urine volume and solute clearance determinations should be obtained at a minimum of every 3 months.

6.3.3 For patients without RKF (defined as urine $Kt/V_{urea} < 0.1$/wk) or for those in whom RKF is unable to be measured accurately:

6.3.3.1 The minimal "delivered" dose of small-solute clearance should be a peritoneal Kt/V_{urea} of at least 1.8/wk.

6.3.3.2 The peritoneal solute clearance should be measured within the first month after starting dialysis and *at least* once every 6 months thereafter.

6.3.4 When calculating Kt/V_{urea}, one should estimate V or TBW by using the sex-specific nomograms based upon the following equations:

$$\text{Males: } TBW = 0.010 \cdot (\text{height} \cdot \text{weight})^{0.68} - 0.37 \cdot \text{weight}$$

$$\text{Females: } TBW = 0.14 \cdot (\text{height} \cdot \text{weight})^{0.64} - 0.35 \cdot \text{weight}$$

6.4 Preservation of RKF:

6.4.1 Techniques that may contribute to the preservation of RKF in pediatric patients receiving PD should be incorporated as a component of dialysis care whenever possible.

6.4.1.1 Nephrotoxic insults in those with normal or impaired kidney function should be assumed, in the absence of direct evidence, to also be nephrotoxic in patients on PD therapy who have RKF and therefore should be avoided.

6.4.1.2 Aminoglycoside antibiotics should be avoided whenever possible to minimize the risk for nephrotoxicity, as well as ototoxicity and vestibular toxicity.

6.4.1.3 "Prekidney" and "postkidney" causes of a decrease in RKF should be considered in the appropriate clinical setting.

6.4.1.4 Infections of the urinary tract should be treated promptly.

6.4.1.5 Diuretics should be used to maximize urinary salt and water excretion.

6.4.1.6 An ACE inhibitor or ARB should be considered in a PD patient who requires antihypertensive medication and has RKF.

6.5 Writing the PD prescription:

6.5.1 In addition to solute clearance, QOL, ultrafiltration/volume control, and possibly the clearance of middle molecules should be considered when writing the PD prescription.

6.5.1.1 The patient's dialysis schedule and QOL as it relates to such issues as school and work attendance/performance should be taken into account when designing the dialysis prescription.

6.5.1.2 To optimize small-solute clearance, minimize cost, and possibly decrease the frequency of exchanges, one should first increase the instilled volume per exchange (target range, 1,000 to 1,200 mL/m^2 BSA; maximum, 1,400 mL/m^2 BSA), as tolerated by the patient, before increasing the number of exchanges per day. The volume of the supine exchange(s) should be increased first because this position has the lowest intra-abdominal pressure. Objective evidence of patient tolerance may require assessment of IPP.

6.5.1.3 The patient's record of PD effluent volume should be reviewed monthly, with particular attention to the drain volume from the overnight dwell of CAPD and daytime dwell of CCPD.

6.5.1.4 Factors to be considered when attempting to optimize total body volume include:

a. Dietary sodium and fluid restriction may be implemented in patients unable to maintain euvolemia/normotension with dialysis alone.

b. In patients with RKF, diuretics may be preferred over increasing the dialysate dextrose concentration to achieve euvolemia.

c. Drain volume should be optimized after the overnight dwell of CAPD and the daytime dwell(s) of CCPD to maximize solute clearance and ultrafiltration volume.

d. In patients who are hypertensive or in whom there is evidence of volume overload, ultrafiltration generally should be positive for all daytime or nighttime exchanges.

e. An effort should be made to determine the lowest possible dialysate dextrose concentration required to achieve the desired ultrafiltration volume.

6.5.1.5 To optimize middle-molecule clearance in patients who have minimal RKF, the PD prescription should preferentially include the use of CCPD with dwells 24 h/d or CAPD. This is recommended even if small-molecule clearance is above target without the longer dwell.

6.5.1.6 The use of NIPD (eg, no daytime dwell) can be considered in pediatric patients who are clinically well, whose combined dialysis prescription and RKF achieves or exceeds the target solute clearance, and who are without evidence of hyperphosphatemia, hyperkalemia, hypervolemia, or acidosis.

6.6 Other aspects of the care of the pediatric PD patient:

6.6.1 All children on PD therapy with anemia should follow the KDOQI Guidelines for Management of Anemia that pertain to pediatrics.[231]

6.6.2 Management of dyslipidemias for prepubertal children on PD therapy should follow recommendations by the National Cholesterol Expert Panel in Children and Adolescents.[232] Postpubertal children or adolescents on PD therapy should follow the pediatric recommendations provided in the KDOQI Clinical Practice Guidelines for Managing Dyslipidemia in CKD.[233]

6.6.3 All children on PD therapy should follow the pediatric-specific recommendations provided in the KDOQI Clinical Practice Guidelines for CVD in Dialysis Patients and the KDOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in CKD.[158,166]

6.6.4 All children on PD therapy should follow the recommendations provided in the KDOQI Clinical Practice Guidelines for Nutrition in Chronic Renal Failure.[35]

RATIONALE

Dialysis Initiation

The gold standard for measurement of GFR is inulin clearance, but this technique is impractical to perform clinically. Whereas the use of such radioisotopic measures as chromium-51, iothalamate sodium ^{125}I, and technetium 99-DTPA are alternative measures to inulin, these techniques are expensive, require multiple blood samples, and are not ideal for frequent monitoring.[234,235]

Table 16. Mean Values of k

Age Group	k (Mean Value)
Low Birth Weight (LBW) infants ≤1 year	0.33
Full-term infants ≤1 year	0.45
Children 2-12 years	0.55
Females 13-21 years	0.55
Males 13-21 years	0.70

A measured C_{Cr} requires a timed urine collection, most often 12 to 24 hours in duration. The accuracy of the assessment as a means of estimating GFR is complicated by the need for a complete urine collection and that creatinine secretion results in overestimation of GFR, especially at lower levels of kidney function.[236,237] At lower levels of GFR, accuracy is improved by measuring both creatinine and urea clearances on the same timed urine collection and averaging the values to obtain the estimated GFR.[238,239]

The accuracy of the GFR estimate by C_{Cr} can be increased by the provision of cimetidine to the patient before the timed urine collection.[239] A study of children showed that as a result of cimetidine's capacity to block the kidney's tubular secretion of creatinine, its use in a formal outpatient protocol is associated with GFR results that approximate those obtained with inulin.[240,241]

The Schwartz formula also overestimates GFR, especially at lower GFR levels, and provides a less accurate means of estimating the target clearance for dialysis consideration than what can be determined with a complete timed urine collection.[242] However, recent pediatric data show that a GFR of 15 mL/min/1.73 m^2 or less estimated by using the Schwartz formula had an excellent negative predictive value for a measured GFR of 20 mL/min/1.73 m^2 by using iothalamate clearance.[243]

Because a timed urine collection often is not possible for smaller non–toilet-trained children, reliance on a serum creatinine–based formula, such as the Schwartz formula, is essential in this subset of patients. The Schwartz formula contains a cofactor that accounts for patient sex and age to incorporate estimates of lean body mass. The Schwartz formula is calculated in the following manner[4,242]:

$$GFR = kL/Pcr$$

where GFR is expressed in milliliters per minute per 1.73 m^2, L represents body length in centimeters, Pcr is plasma creatinine in milligrams per deciliter, and *k,* a constant of proportionality, is a function of urinary creatinine excretion per unit of body size (see Table 16).

Finally, a variety of signs and symptoms may be present in the pediatric patient with CKD stage 4 (GFR, 15 to 29 mL/min/1.73 m^2) that are not routinely associated with the presence of uremia, but that remain unresponsive to medical and/or dietary therapy. A trial of dialysis may on occasion result in marked clinical improvement.

Modality Selection

PD is the preferred initial long-term dialysis modality worldwide for the pediatric patient with CKD stage 5.[244,245] Its use is particularly advantageous in the very small patient for whom maintenance of a functional and complication-free vascular access can be problematic. The provision of PD, often in association with the use of an automated cycling device, also facilitates regular school attendance for most age-appropriate children.[245] The use of PD is preferred over HD when there are contraindications to the use of anticoagulation, in children who have cardiovascular instability, and in children who live far from a pediatric HD center.

However, there are absolute and relative contraindications to the use of PD in children that include the following[246]:

Absolute contraindications:

- Omphalocele
- Gastroschisis
- Bladder extrophy
- Diaphragmatic hernia
- Obliterated peritoneal cavity
- Peritoneal membrane failure

Relative contraindications:

- Inadequate living situation for home dialysis
- Lack of appropriate caregiver
- Impending/recent major abdominal surgery
- Imminent living-related donor transplantation (within 6 months of dialysis initiation)

Recognition of the burden of care for families that coexists with the provision of this home therapy is paramount so that appropriate support systems may be put in place.[247] Assessment of the patient's and caregiver's perception of QOL may aid in this process.[246A]

PD Solute Clearance Targets and Measurements

The clinical status of the pediatric patient should be monitored closely as an important qualitative means of determining whether the patient is receiving an adequate quantity of dialysis. Irrespective of the delivered dose of dialysis, adequate dialysis likely is provided if the patient's clinical status is characterized by adequate growth, blood pressure control, and nutritional status; avoidance of hypovolemia and sodium depletion; and adequate psychomotor development.[246,248]

Clinical manifestations of inadequate dialysis may include the following:

- CHF
- Hyperphosphatemia/excessive serum calcium $\times$ phosphorus product
- Uncontrolled hypertension/hypervolemia
- Overt uremia (uremic pericarditis, pleuritis)

- Repeated hyperkalemic episodes
- Clinical or biochemical signs of malnutrition or wasting
- Poor school performance

Factors contributing to inadequate dialysis include:

- Loss of RKF
- Prescription inadequate for peritoneal membrane transport characteristics
- Reduced peritoneal surface area caused by extensive intra-abdominal adhesions
- Loss of membrane solute transport/ultrafiltration capacity because of peritonitis
- Noncompliance with PD prescription
- Poorly functioning PD catheter

Current clinical opinion supports the recommendation that the target "delivered" solute clearance in pediatric patients should meet or exceed adult standards. The term "delivered" refers to the actual dose the patient is receiving based on measurement, in contrast to an estimated value using a kinetic modeling program.[151,156] Data from pediatric and adult patients found serum albumin level to be a predictor of patient survival, and a Kt/V_{urea} of 1.8 or greater in adult PD patients has been associated with better serum albumin values.[55,249] The ADEMEX Study did not show a clinical benefit associated with Kt/V_{urea} greater than 1.7/wk in adult CAPD patients, whereas other studies provided evidence for a recommended minimal Kt/V_{urea} greater than 1.7/wk and an optimal Kt/V_{urea} of 1.8/wk based on survival data in anuric adult CAPD patients.[38,39,70] No similar large-scale studies have been performed in children. Pediatric studies have presented data suggestive of a correlation between patient outcome (especially growth) and total solute clearance; however, the number of patients in these and other pediatric studies is small and the potential role of RKF can be confounding, and thus data correlating solute clearance to outcome cannot be considered definitive.[250,251] Nevertheless, it is recommended that solute clearance assessments take place *at least* every 6 months in all cases and that more frequent assessments be conducted when dialysis clearance may have been compromised (eg, after peritonitis), there is a progressive loss of RKF, or there is clinical evidence of inadequate dialysis.

Historically, both Kt/V_{urea} and C_{Cr} have served as measures of dialysis clearance. In addition, the averaged urea and C_{Cr} from a timed urine collection has been recommended as the most accurate means to estimate RKF and remains a preferred approach to estimate GFR when considering dialysis therapy initiation.[238,239] Nevertheless, determination of dialysis and urine Kt/V_{urea} alone currently is recommended for follow-up based upon the simplicity of the calculation and because studies of adult patients on PD therapy have not provided evidence of a benefit in terms of patient outcome when expressing clearance in any manner other than Kt/V_{urea}.[252,253] The age-related differences in the residual urine volume of children with CKD stage 5 precludes duplication of the adult preference to universally characterize the presence of RKF as urine volume greater than 100 mL/d.

Accurate estimation of TBW or V is a critical component of the dialysis prescription in PD. Because gold-standard isotope dilution techniques are laborious, cost-ineffective, and

not widely available, anthropometric prediction equations based on height and weight commonly are used to determine TBW.[254] During childhood, complex changes in body composition occur that necessitate the use of appropriate allometric formulae. Whereas such equations have been established in healthy populations, recent studies showed that the use of these equations routinely overestimates TBW in pediatric patients receiving PD.[255–257] Conversely, the recent determination of TBW by heavy water (H_2O^{18} or D_2O) dilution in 64 pediatric patients receiving PD has allowed for the development of TBW prediction equations that perform equally well in male and female, North American and European, obese and nonobese, and growth-retarded and normally sized children.[148]

The sex-specific nomograms designed to estimate TBW, which are based upon the prediction equations, are shown in Table 17 and Table 18.

Because the height · weight parameter also predicts BSA, use of the Gehan and George equation for BSA allows for TBW-estimating equations that can be simplified, but with slightly less precision, compared with the best fitting equations to:

$$\text{Male: TBW} = 20.88 \bullet \text{BSA} - 4.29$$

$$\text{Females: TBW} = 16.92 \bullet \text{BSA} - 1.81$$

Whereas several approaches to the calculation of BSA are used in pediatrics, the Gehan and George equation for BSA was derived from the greatest number of study subjects.[258,259] The Gehan and George equation is as follows:

$$\text{BSA } (m^2) = 0.0235 \bullet (\text{height [cm]})^{0.42246} \bullet (\text{weight [kg]})^{0.51456}$$

Based on this equation, BSA can be determined by height and weight by referring to Table 19.

Preservation of RKF

There are no large-scale studies in pediatrics that provide evidence of a correlation between RKF and patient outcome in children receiving PD. However, in a single-center observation of a pediatric PD population, it was shown that superior growth velocity occurred in a group of children with RKF versus a group of children without RKF despite the achievement of similar mean total solute clearance in the 2 groups of patients.[250] Thus, it is possible that growth, as well as achievement of solute clearance goals, benefits from RKF and emphasizes the need to prevent nephrotoxic insults whenever possible. In addition, there is evidence that pediatric patients on PD therapy lose RKF at a slower rate than patients on HD therapy.[260]

While there is no experience regarding the use of ACE inhibitors or ARBs in children with CKD stage 5 similar to that in adults, use of an ACE inhibitor in children with CKD has been associated with marked slowing of kidney deterioration.[99,100,261] In the setting of CKD stage 5, close monitoring for the presence of hyperkalemia is mandatory when an ACE inhibitor or ARB is used.[262]

Table 17. Male Total Body Water (L) Nomograms

Weight (kg) \ Height (cm)	50	54	58	62	66	70	74	78	82	86	90	94	98	102	106	110	114
2	1.6	1.7	1.8	1.9													
3	1.9	2.1	2.2	2.4													
4	2.2	2.4	2.6	2.8	3.0												
5	2.4	2.7	2.9	3.1	3.3												
6	2.6	2.9	3.1	3.4	3.6	3.9	4.1										
7	2.8	3.1	3.4	3.6	3.9	4.2	4.4	4.7	4.9								
8	2.9	3.2	3.5	3.9	4.1	4.4	4.7	5.0	5.3	5.5	5.8						
9				4.0	4.4	4.7	5.0	5.3	5.6	5.9	6.2	6.5	6.7				
10				4.2	4.6	4.9	5.2	5.6	5.9	6.2	6.5	6.8	7.1	7.4	7.7		
11				4.4	4.8	5.1	5.5	5.8	6.2	6.5	6.8	7.1	7.5	7.8	8.1	8.4	8.7
12				4.5	4.9	5.3	5.7	6.0	6.4	6.8	7.1	7.5	7.8	8.1	8.5	8.8	9.1
13								6.3	6.6	7.0	7.4	7.8	8.1	8.5	8.8	9.2	9.5
14								6.5	6.9	7.3	7.7	8.0	8.4	8.8	9.2	9.5	9.9
15								6.7	7.1	7.5	7.9	8.3	8.7	9.1	9.5	9.9	10.2
16								6.8	7.3	7.7	8.1	8.6	9.0	9.4	9.8	10.2	10.6
17											8.4	8.8	9.2	9.7	10.1	10.5	10.9
18											8.6	9.0	9.5	9.9	10.4	10.8	11.2
19											8.8	9.3	9.7	10.2	10.6	11.1	11.5
20											9.0	9.4	9.9	10.4	10.9	11.3	11.8

Table 17 (cont'd). Male Total Body Water (L) Nomograms

Weight (kg) / Height (cm)

	106	110	114	118	122	126	130	134	138	142	146	150	154	158	162	166	170	174	178	182	186	190
20	10.9	11.3	11.8	12.3	12.7	13.2	13.6	14.0	14.5	14.9	15.3	15.7										
22	11.4	11.9	12.4	12.8	13.3	13.8	14.3	14.7	15.2	15.7	16.1	16.6										
24	11.8	12.3	12.9	13.4	13.9	14.4	14.9	15.4	15.9	16.4	16.8	17.3	17.8	18.3	18.7							
26	12.2	12.8	13.3	13.9	14.4	15.0	15.5	16.0	16.5	17.0	17.5	18.0	18.5	19.0	19.5							
28	12.6	13.2	13.8	14.4	14.9	15.5	16.0	16.6	17.1	17.7	18.2	18.7	19.3	19.8	20.3	20.8	21.3					
30	13.0	13.6	14.2	14.8	15.4	16.0	16.6	17.1	17.7	18.3	18.8	19.4	19.9	20.5	21.0	21.6	22.1					
32	13.3	14.0	14.6	15.2	15.8	16.5	17.1	17.7	18.3	18.8	19.4	20.0	20.6	21.2	21.7	22.3	22.9	23.4	24.0			
34	13.6	14.3	15.0	15.6	16.3	16.9	17.5	18.2	18.8	19.4	20.0	20.6	21.2	21.8	22.4	23.0	23.6	24.2	24.7			
36	13.9	14.6	15.3	16.0	16.7	17.3	18.0	18.7	19.3	19.9	20.6	21.2	21.8	22.4	23.1	23.7	24.3	24.9	25.5	26.1	26.6	
38	14.2	14.9	15.7	16.4	17.1	17.8	18.4	19.1	19.8	20.4	21.1	21.8	22.4	23.0	23.7	24.3	24.9	25.6	26.2	26.8	27.4	
40			16.0	16.7	17.4	18.1	18.8	19.5	20.2	20.9	21.6	22.3	23.0	23.6	24.3	24.9	25.6	26.2	26.9	27.5	28.1	28.8
42			16.3	17.0	17.8	18.5	19.2	20.0	20.7	21.4	22.1	22.8	23.5	24.2	24.9	25.5	26.2	26.9	27.5	28.2	28.8	29.5
44			16.6	17.3	18.1	18.9	19.6	20.4	21.1	21.8	22.6	23.3	24.0	24.7	25.4	26.1	26.8	27.5	28.2	28.8	29.5	30.2
46			16.8	17.6	18.4	19.2	20.0	20.8	21.5	22.3	23.0	23.8	24.5	25.2	26.0	26.7	27.4	28.1	28.8	29.5	30.2	30.9
48			17.1	17.9	18.7	19.5	20.3	21.1	21.9	22.7	23.5	24.2	25.0	25.7	26.5	27.2	27.9	28.7	29.4	30.1	30.8	31.5
50			17.3	18.2	19.0	19.8	20.7	21.5	22.3	23.1	23.9	24.7	25.4	26.2	27.0	27.7	28.5	29.2	30.0	30.7	31.5	32.2
52						20.1	21.0	21.8	22.6	23.5	24.3	25.1	25.9	26.7	27.5	28.2	29.0	29.8	30.6	31.3	32.1	32.8
54						20.4	21.3	22.1	23.0	23.8	24.7	25.5	26.3	27.1	27.9	28.7	29.5	30.3	31.1	31.9	32.7	33.4
56						20.7	21.6	22.5	23.3	24.2	25.0	25.9	26.7	27.6	28.4	29.2	30.0	30.8	31.7	32.4	33.2	34.0
58						20.9	21.8	22.8	23.7	24.5	25.4	26.3	27.1	28.0	28.8	29.7	30.5	31.4	32.2	33.0	33.8	34.6
60						21.2	22.1	23.1	24.0	24.9	25.8	26.7	27.5	28.4	29.3	30.1	31.0	31.8	32.7	33.5	34.4	35.2
62						21.4	22.4	23.3	24.3	25.2	26.1	27.0	27.9	28.8	29.7	30.6	31.5	32.3	33.2	34.0	34.9	35.7
64						21.7	22.6	23.6	24.6	25.5	26.4	27.4	28.3	29.2	30.1	31.0	31.9	32.8	33.7	34.5	35.4	36.3
66									24.8	25.8	26.8	27.7	28.6	29.6	30.5	31.4	32.3	33.2	34.1	35.0	35.9	36.8
68									25.1	26.1	27.1	28.0	29.0	30.0	30.9	31.8	32.8	33.7	34.6	35.5	36.4	37.3
70									25.4	26.4	27.4	28.4	29.3	30.3	31.3	32.2	33.2	34.1	35.1	36.0	36.9	37.8
72									25.6	26.6	27.7	28.7	29.7	30.7	31.6	32.6	33.6	34.5	35.5	36.4	37.4	38.3
74									25.9	26.9	27.9	29.0	30.0	31.0	32.0	33.0	34.0	34.9	35.9	36.9	37.8	38.8
76									26.1	27.2	28.2	29.3	30.3	31.3	32.3	33.3	34.4	35.3	36.3	37.3	38.3	39.3
78									26.3	27.4	28.5	29.5	30.6	31.6	32.7	33.7	34.7	35.7	36.7	37.7	38.7	39.7
80									26.5	27.6	28.7	29.8	30.9	31.9	33.0	34.1	35.1	36.1	37.1	38.2	39.2	40.2

Table 18. Female Total Body Water (L) Nomograms

Weight (kg) \ Height (cm)	50	54	58	62	66	70	74	78	82	86	90	94	98	102	106	110	114
2	2.0	2.1	2.2	2.4													
3	2.4	2.6	2.8	2.9													
4	2.8	3.0	3.2	3.4	3.6												
5	3.1	3.3	3.5	3.8	4.0												
6	3.3	3.6	3.8	4.1	4.3	4.6	4.8										
7	3.5	3.8	4.1	4.4	4.8	4.9	5.2	5.5	5.7								
8	3.7	4.0	4.3	4.6	4.9	5.2	5.5	5.8	6.1	6.4	6.6						
9				4.9	5.2	5.5	5.8	6.1	6.4	6.7	7.0	7.3	7.6				
10				5.1	5.4	5.8	6.1	6.4	6.8	7.1	7.4	7.7	8.0	8.3	8.6		
11				5.3	5.6	6.0	6.4	6.7	7.1	7.4	7.7	8.1	8.4	8.7	9.0	9.3	9.6
12				5.4	5.8	6.2	6.6	7.0	7.3	7.7	8.0	8.4	8.7	9.1	9.4	9.7	10.0
13								7.2	7.6	8.0	8.3	8.7	9.1	9.4	9.8	10.1	10.4
14								7.4	7.8	8.2	8.6	9.0	9.4	9.7	10.1	10.5	10.8
15								7.6	8.0	8.5	8.9	9.3	9.7	10.0	10.4	10.8	11.2
16								7.8	8.3	8.7	9.1	9.5	9.9	10.3	10.7	11.1	11.5
17											9.3	9.8	10.2	10.6	11.0	11.4	11.8
18											9.6	10.0	10.5	10.9	11.3	11.7	12.2
19											9.8	10.2	10.7	11.1	11.6	12.0	12.5
20											10.0	10.4	10.9	11.4	11.8	12.3	12.7

Table 18 (cont'd). Female Total Body Water (L) Nomograms

Weight (kg) \ Height (cm)	106	110	114	118	122	126	130	134	138	142	146	150	154	158	162	166	170	174	178	182	186	190
20	11.8	12.3	12.7	13.2	13.6	14.0	14.5	14.9	15.3	15.7	16.1	16.5										
22	12.3	12.8	13.3	13.7	14.2	14.7	15.1	15.6	16.0	16.4	16.9	17.3										
24	12.8	13.3	13.8	14.3	14.8	15.2	15.7	16.2	16.7	17.1	17.6	18.0	18.5	18.9	19.4							
26	13.2	13.7	14.2	14.8	15.3	15.8	16.3	16.8	17.3	17.8	18.3	18.7	19.2	19.7	20.1							
28	13.6	14.1	14.7	15.2	15.8	16.3	16.8	17.3	17.9	18.4	18.9	19.4	19.9	20.4	20.9	21.3	21.8					
30	13.9	14.5	15.1	15.7	16.2	16.8	17.3	17.9	18.4	18.9	19.5	20.0	20.5	21.0	21.5	22.0	22.5					
32	14.3	14.9	15.5	16.1	16.6	17.2	17.8	18.4	18.9	19.5	20.0	20.6	21.1	21.7	22.2	22.7	23.2	23.7	24.3			
34	14.6	15.2	15.8	16.4	17.0	17.7	18.2	18.8	19.4	20.0	20.6	21.1	21.7	22.3	22.8	23.4	23.9	24.4	25.0			
36	14.8	15.5	16.2	16.8	17.4	18.1	18.7	19.3	19.9	20.5	21.1	21.7	22.3	22.8	23.4	24.0	24.5	25.1	25.6	26.2	26.7	
38	15.1	15.8	16.5	17.1	17.8	18.4	19.1	19.7	20.3	21.0	21.6	22.2	22.8	23.4	24.0	24.6	25.1	25.7	26.3	26.9	27.4	
40			16.8	17.4	18.1	18.8	19.5	20.1	20.7	21.4	22.0	22.7	23.3	23.9	24.5	25.1	25.7	26.3	26.9	27.5	28.1	28.6
42			17.0	17.7	18.4	19.1	19.8	20.5	21.1	21.8	22.5	23.1	23.8	24.4	25.0	25.7	26.3	26.9	27.5	28.1	28.7	29.3
44			17.3	18.0	18.7	19.5	20.2	20.9	21.5	22.2	22.9	23.6	24.2	24.9	25.5	26.2	26.8	27.4	28.1	28.7	29.3	29.9
46			17.5	18.3	19.0	19.8	20.5	21.2	21.9	22.6	23.3	24.0	24.7	25.3	26.0	26.7	27.3	28.0	28.6	29.3	29.9	30.5
48			17.8	18.5	19.3	20.0	20.8	21.5	22.3	23.0	23.7	24.4	25.1	25.8	26.5	27.2	27.8	28.5	29.2	29.8	30.5	31.1
50			18.0	18.8	19.6	20.3	21.1	21.8	22.6	23.3	24.1	24.8	25.5	26.2	26.9	27.6	28.3	29.0	29.7	30.4	31.0	31.7
52						20.6	21.4	22.1	22.9	23.7	24.4	25.2	25.9	26.6	27.4	28.1	28.8	29.5	30.2	30.9	31.6	32.2
54						20.8	21.6	22.4	23.2	24.0	24.8	25.5	26.3	27.0	27.8	28.5	29.2	29.9	30.7	31.4	32.1	32.8
56						21.1	21.9	22.7	23.5	24.3	25.1	25.9	26.6	27.4	28.2	28.9	29.7	30.4	31.1	31.9	32.6	33.3
58						21.3	22.1	23.0	23.8	24.6	25.4	26.2	27.0	27.8	28.5	29.3	30.1	30.8	31.6	32.3	33.1	33.8
60						21.5	22.4	23.2	24.1	24.9	25.7	26.5	27.3	28.1	28.9	29.7	30.5	31.3	32.0	32.8	33.5	34.3
62						21.7	22.6	23.4	24.3	25.2	26.0	26.8	27.7	28.5	29.3	30.1	30.9	31.7	32.4	33.2	34.0	34.8
64						21.9	22.8	23.7	24.6	25.4	26.3	27.1	28.0	28.8	29.6	30.4	31.3	32.1	32.9	33.6	34.4	35.2
66									24.8	25.7	26.5	27.4	28.3	29.1	30.0	30.8	31.6	32.4	33.2	34.1	34.9	35.7
68									25.0	25.9	26.8	27.7	28.6	29.4	30.3	31.1	32.0	32.8	33.6	34.5	35.3	36.1
70									25.2	26.1	27.0	27.9	28.8	29.7	30.6	31.5	32.3	33.2	34.0	34.9	35.7	36.5
72									25.4	26.4	27.3	28.2	29.1	30.0	30.9	31.8	32.7	33.5	34.4	35.2	36.1	36.9
74									25.6	26.6	27.5	28.4	29.4	30.3	31.2	32.1	33.0	33.9	34.7	35.6	36.5	37.3
76									25.8	26.8	27.7	28.7	29.6	30.6	31.5	32.4	33.3	34.2	35.1	36.0	36.8	37.7
78									26.0	27.0	27.9	28.9	29.9	30.8	31.7	32.7	33.6	34.5	35.4	36.3	37.2	38.1
80									26.2	27.2	28.1	29.1	30.1	31.1	32.0	33.0	33.9	34.8	35.7	36.7	37.6	38.5

Table 19. Body Surface Area

Weight (kg)

Height (cm)

	50	54	58	62	66	70	74	78	82	86	90	94	98	102	106	110	114
2	0.18	0.19	0.19	0.19	0.20	0.20	0.21	0.21	0.22	0.22	0.22	0.23	0.23	0.24	0.24	0.24	0.25
3	0.22	0.22	0.23	0.24	0.24	0.25	0.25	0.26	0.27	0.27	0.28	0.28	0.29	0.29	0.30	0.30	0.31
4	0.25	0.26	0.27	0.27	0.28	0.29	0.30	0.30	0.31	0.31	0.32	0.33	0.33	0.34	0.34	0.35	0.35
5	0.28	0.29	0.30	0.31	0.32	0.32	0.33	0.34	0.35	0.35	0.36	0.37	0.37	0.38	0.39	0.39	0.40
6	0.31	0.32	0.33	0.34	0.35	0.36	0.36	0.37	0.38	0.39	0.40	0.40	0.41	0.42	0.42	0.43	0.44
7	0.33	0.34	0.36	0.37	0.38	0.38	0.39	0.40	0.41	0.42	0.43	0.44	0.44	0.45	0.46	0.47	0.47
8	0.36	0.37	0.38	0.39	0.40	0.41	0.42	0.43	0.44	0.45	0.46	0.47	0.48	0.48	0.49	0.50	0.51
9	0.38	0.39	0.40	0.42	0.43	0.44	0.45	0.46	0.47	0.48	0.49	0.50	0.51	0.51	0.52	0.53	0.54
10	0.40	0.41	0.43	0.44	0.45	0.46	0.47	0.48	0.49	0.50	0.51	0.52	0.53	0.54	0.55	0.56	0.57
11	0.42	0.44	0.45	0.46	0.47	0.48	0.50	0.51	0.52	0.53	0.54	0.55	0.56	0.57	0.58	0.59	0.60
12	0.44	0.46	0.47	0.48	0.50	0.51	0.52	0.53	0.54	0.55	0.56	0.58	0.58	0.59	0.60	0.61	0.62
13	0.46	0.47	0.49	0.50	0.52	0.53	0.54	0.55	0.57	0.58	0.59	0.60	0.61	0.62	0.63	0.64	0.65
14	0.48	0.49	0.51	0.52	0.54	0.55	0.56	0.58	0.59	0.60	0.61	0.62	0.63	0.64	0.66	0.67	0.68
15	0.49	0.51	0.53	0.54	0.56	0.57	0.58	0.60	0.61	0.62	0.63	0.65	0.66	0.67	0.68	0.69	0.70
16	0.51	0.53	0.54	0.56	0.57	0.59	0.60	0.62	0.63	0.64	0.65	0.67	0.68	0.69	0.70	0.71	0.72
17	0.53	0.54	0.56	0.58	0.59	0.61	0.62	0.64	0.65	0.66	0.68	0.69	0.70	0.71	0.72	0.74	0.75
18	0.54	0.56	0.58	0.59	0.61	0.63	0.64	0.66	0.67	0.68	0.70	0.71	0.72	0.73	0.75	0.76	0.77
19	0.56	0.58	0.59	0.61	0.63	0.64	0.66	0.67	0.69	0.70	0.72	0.73	0.74	0.75	0.77	0.78	0.79
20	0.57	0.59	0.61	0.63	0.64	0.66	0.68	0.69	0.71	0.72	0.73	0.75	0.76	0.77	0.79	0.80	0.81

Table 19 (cont'd). Body Surface Area

Weight (kg) \ Height (cm)	106	110	114	118	122	126	130	134	138	142	146	150	154	158	162	166	170
20	0.79	0.80	0.81	0.82	0.84	0.85	0.86	0.87	0.88	0.89	0.90	0.91	0.92	0.93	0.94	0.95	0.96
22	0.83	0.84	0.85	0.87	0.88	0.89	0.90	0.91	0.92	0.94	0.95	0.96	0.97	0.98	0.99	1.00	1.01
24	0.86	0.88	0.89	0.90	0.92	0.93	0.94	0.95	0.97	0.98	0.99	1.00	1.01	1.02	1.03	1.05	1.06
26	0.90	0.92	0.93	0.94	0.96	0.97	0.98	0.99	1.01	1.02	1.03	1.04	1.06	1.07	1.08	1.09	1.10
28	0.94	0.95	0.97	0.98	0.99	1.01	1.02	1.03	1.05	1.06	1.07	1.08	1.10	1.11	1.12	1.13	1.14
30	0.97	0.99	1.00	1.01	1.03	1.04	1.06	1.07	1.08	1.10	1.11	1.12	1.14	1.15	1.16	1.17	1.18
32	1.00	1.02	1.03	1.05	1.06	1.08	1.09	1.11	1.12	1.13	1.15	1.16	1.17	1.19	1.20	1.21	1.22
34	1.03	1.05	1.07	1.08	1.10	1.11	1.13	1.14	1.16	1.17	1.18	1.20	1.21	1.22	1.24	1.25	1.26
36	1.07	1.08	1.10	1.11	1.13	1.15	1.16	1.18	1.19	1.21	1.22	1.23	1.25	1.26	1.27	1.29	1.30
38	1.10	1.11	1.13	1.15	1.16	1.18	1.19	1.21	1.22	1.24	1.25	1.27	1.28	1.30	1.31	1.32	1.34
40	1.12	1.14	1.16	1.18	1.19	1.21	1.23	1.24	1.26	1.27	1.29	1.30	1.32	1.33	1.35	1.36	1.37
42	1.15	1.17	1.19	1.21	1.22	1.24	1.26	1.27	1.29	1.30	1.32	1.34	1.35	1.37	1.38	1.39	1.41
44	1.18	1.20	1.22	1.24	1.25	1.27	1.29	1.30	1.32	1.34	1.35	1.37	1.38	1.40	1.41	1.43	1.44
46	1.21	1.23	1.25	1.26	1.28	1.30	1.32	1.33	1.35	1.37	1.38	1.40	1.42	1.43	1.45	1.46	1.48
48	1.24	1.25	1.27	1.29	1.31	1.33	1.35	1.36	1.38	1.40	1.41	1.43	1.45	1.46	1.48	1.49	1.51
50	1.26	1.28	1.30	1.32	1.34	1.36	1.38	1.39	1.41	1.43	1.44	1.46	1.48	1.49	1.51	1.52	1.54
52	1.29	1.31	1.33	1.35	1.37	1.38	1.40	1.42	1.44	1.46	1.47	1.49	1.51	1.52	1.54	1.56	1.57
54	1.31	1.33	1.35	1.37	1.39	1.41	1.43	1.45	1.47	1.49	1.50	1.52	1.54	1.55	1.57	1.58	1.60
56	1.34	1.36	1.38	1.40	1.42	1.44	1.46	1.48	1.49	1.51	1.53	1.55	1.57	1.58	1.60	1.62	1.63
58	1.36	1.38	1.40	1.42	1.44	1.46	1.48	1.50	1.52	1.54	1.56	1.58	1.59	1.61	1.63	1.65	1.66
60	1.39	1.41	1.43	1.45	1.47	1.49	1.51	1.53	1.55	1.57	1.59	1.60	1.62	1.64	1.66	1.67	1.69

Writing the PD prescription

Both CAPD and APD are used by children, and the prescription designed for either modality is best tailored to the needs of the individual patient. APD is the preferred PD modality in children, in large part because its use is characterized by freedom from procedures during the daytime hours.[245,263] The pediatric PD patient's QOL and the influence that the dialysis prescription has on it is an issue that should be reassessed regularly because of the impact that CKD can have on the child's overall development. Although there are not yet any validated measures of QOL designed for the pediatric CKD stage 5 population, the PedsQL™ 4.0 Generic Core Scales and the Child Health Questionnaire have both been used successfully in the pediatric dialysis population.[246A,264,265]

Pediatric data have provided evidence that the prescription of an exchange volume that results in an exceedingly high IPP may result in patient intolerance and poor ultrafiltration.[266] Whereas the target range for the exchange volume of patients older than 2 years is 1,000 to 1,200 mL/m^2 BSA, the initial prescribed volume should be somewhat lower for smaller infants (~600 to 800 mL/m^2 BSA). A stepwise increase in volume as tolerated by the patient usually is possible.

While the limitation of dietary sodium in children may have a positive influence on total body volume, this recommendation should be instituted with caution in patients with high RKF and/or dialysis-related sodium losses. Salt depletion may result in hypotension and impaired growth.[267]

The removal of "middle molecules" and low-molecular-weight proteins ideally also should be taken into account in the prescription process because of the influence it may have on clinical outcome, especially in patients without RKF.[248] However, few data exist on the topic in pediatrics, prompting it to currently have a minor role in prescription considerations for children.[268]

Although the PD prescription is characterized most often by 24-hour dwells, in some circumstances, NIPD without the use of a daytime dwell can be used effectively. Its use requires that the patient's clinical status be monitored closely and consideration be given to a 24-hour dwell prescription if NIPD is not fully effective. This recommendation has been made previously by the European Pediatric PD Working Group.[269]

LIMITATIONS

No large-scale prospective study has been conducted in children on PD therapy that correlates solute removal (PD and RKF) with patient outcome. This precludes the ability to make an evidence-based recommendation regarding the target solute clearance.

Few data are available for children that compare the impact of RKF versus peritoneal solute removal on patient outcome.

Although data are available from the adult CKD stage 5 population showing the benefit of ACE-inhibitor and ARB therapy as a means of preserving RKF, no similar pediatric data are available.

The ability to assess the QOL of the pediatric PD patient and his or her family is limited by the absence of a QOL tool that has been validated in the pediatric CKD stage 5 population.

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 on the need for research to provide additional evidence.

The recognized lack of prospective randomized trials and level A medical evidence was noted when the original KDOQI Guidelines for PD Adequacy were formulated. As a result, most of the guidelines were opinion based, and important areas for research were identified. Some of those questions have been answered with well-conducted, prospective, randomized trials so that new guidelines can be formulated with grade A and B medical evidence. Subsequent studies have identified further questions and deficiencies in current medical knowledge that will hopefully stimulate further research.

CRITICAL RESEARCH RECOMMENDATIONS

Guideline 1. Initiation of Dialysis

Although it is recognized that the patient's clinical condition at the start of KRT is an important predictor of outcome, there are no data to confirm whether an "earlier" (in terms of kidney progression) or a "healthier" (less advanced comorbidities) start results in a survival advantage or just a lead-time bias. Furthermore, is the answer to that question dependent on prior rate of progression of kidney disease, cause of kidney disease, the same for different ethnic groups, or dependent on comorbidities present? Given the cost of KRT to society, it is important to know whether, in general, the timing of the start of dialysis therapy improves total lifespan or only increases time on dialysis therapy, but not total lifespan. If it is the latter, data to show that the patient otherwise would tend to be healthier with less hospitalization, better QOL, or rehabilitation also would be important to know.

Guideline 2. PD Solute Clearance Targets and Measurements

It now is well documented that the presence of RKF offers the typical patient on KRT an important survival advantage. What is not known is why that is true. Is it caused by better blood pressure or volume control, more small-solute removal, removal of middle molecules, or some other poorly recognized function of metabolic or paracrine function of the kidney tubules? Additional research to define the effects of RKF would be most important. Results may influence clinical practice, guidelines on initiation of dialysis therapy (can it be done in an incremental manner?), and further determine how one best includes the residual kidney component of total solute clearance in dose calculations.

As noted in the text of these guidelines, 2 recent prospective randomized trials suggested that, over the range of solute clearance studies and using current standard PD technologies (mainly CAPD), trying to achieve higher solute clearance goals had little clinical benefit for the population as a whole. Therefore, considerably more research is needed in the area of adequacy of PD. Additional randomized trials, optimally multicentered, to

examine different PD doses are needed to evaluate lower Kt/V_{urea} in populations with larger patients with more comorbidity. A study that compares a group that maintains a peritoneal Kt/V_{urea} of 1.7 from the start of dialysis therapy (disregarding RKF) with a group that has a total Kt/V_{urea} of 1.7 (kidney plus peritoneal, which would require starting PD therapy with a minimal prescription with subsequent adjustment upward as RKF is lost) would be helpful. In addition, a randomized trial of different levels of small-molecule clearances is needed specifically for anuric patients on PD therapy. Trials with a longer follow-up than 2 years with assessment of nerve conduction to evaluate for neuropathy would be helpful. Markers of middle-molecule clearances also should be obtained long term. A randomized study to evaluate the influence of middle-molecule clearance or of full- versus partial-duration day dwells on patient outcomes would be valuable.

Trials are needed in APD, with both dry day and wet days. A trial that compares outcomes with beginning PD on APD with a dry day versus beginning PD with a wet day (controlling for peritoneal dose), with the subsequent adjustment of the prescription (including the addition of a wet day), would be informative in evaluating the potential benefit of a dry abdomen for part of the day on protection of the peritoneal membrane and immune function. Such a study would need to include markers of the peritoneal membrane, as well as determination of middle molecules and neuropathy.

Studies must be designed that separate the effects of volume control from those of small-molecule clearances. It is clear from the studies that have been done that volume overload sometimes is a consequence of using a limited number of exchanges in CAPD and perhaps a consequence of excessively short nighttime exchanges in APD, in which the ultrafiltration volume is likely to be 50% sodium free.

Because increasing small-molecule clearance does not appear to be the path to improved survival, studies investigating other maneuvers to decrease mortality should be investigated. Attention should be focused on specific causes of mortality. These studies could include use of an ACE inhibitor in combination with a lipid-lowering drug versus ACE inhibitor alone, monthly follow-up to assess and adjust the prescription to maximize volume status versus less frequent visits, and to evaluate cardiovascular deaths. Anuric patients are more likely to die a sudden death.[69] Data from the same group indicate that hypokalemia is a risk factor for death; in this study, hypokalemia was defined by 3 measurements of potassium during 12 weeks, and sudden death was not more frequent in this group.[270] Therefore, it seems possible that hypokalemia might be more common in anuric patients, possibly because of dietary and nutritional issues, and contribute to sudden death, but this needs to be studied.

Another area that might prove fruitful to decrease morbidity and mortality is further research on decreasing the risk for, and managing, peritonitis. The risk for death related to peritonitis is variable from a low of 3% of deaths in Canada to 16.6% of deaths in Hong Kong.[69] Aggressive catheter removal for refractory peritonitis versus delayed catheter removal (in an attempt to decrease mortality related to peritonitis) may result in a decrease in peritonitis-related deaths. Peritonitis remains the leading cause of technique failure[271] and affects peritoneal function during the first year on PD therapy.[272] Additional research on training methods and exit-site care may prove fruitful.

Last, studies of maneuvers to improve adherence with the prescription and diet are much needed in PD patients, especially in such countries as the United States, where adherence is less than optimal. Such maneuvers might include closer monitoring, treatment of depression, evaluation of supplies with home visits, etc.

Guideline 3. Preservation of RKF

Rigorous studies are needed to examine whether the use of radiocontrast dye affects RKF in dialysis patients and whether renoprotective strategies in the nondialysis population also apply to those on dialysis therapy. Although controversial, it was suggested that the rate of decrease in RKF in those on APD therapy compared with those on CAPD therapy is faster. More data are needed. Because of financial issues and ease of administration, use of aminoglycoside antibiotics for the treatment of peritonitis has been recommended. Therefore, data about whether long- or short-term use of aminoglycosides is associated with a more rapid decrease in RKF would be helpful. The USRDS analysis[80] showed an association between use of ACE inhibitors and also use of calcium channel blockers with better preservation of RKF. Subsequent studies examined ACE inhibitors and ARBs, but not the use of calcium channel blockers; therefore, additional studies are needed. Clinical evaluation of the continuing use of immunosuppressive therapy (other than calcineurin inhibitors) to maintain residual kidney allograft function in patients on dialysis therapy is lacking. Also unclear is whether the benefit of attaining normotension by vigorous ultrafiltration is offset by the decrease in RKF from the attendant volume depletion.

Guideline 4. Maintenance of Euvolemia

Randomized trials to determine optimal blood pressure targets for PD patients are required. Larger randomized trials looking at the effect of newer dialysis solutions on important patient outcomes also would be helpful. Studies looking at the relationship between peritoneal hypertonic glucose exposure and metabolic and cardiovascular outcomes, as well as patient survival, would be valuable.

Guideline 5. Quality Improvement Programs

CQI programs were shown to improve specific outcomes for subgroups of patients, such as peritonitis rates, exit-site infection rates, technique failure rates, etc. It would be important to develop a better understanding about which factors also improve patient well-being and satisfaction with their modality. Current guidelines recommend assessing peritoneal transport status by using PET. They subsequently recommend a hypertonic dwell (4.25% dextrose) to work up a patient with ultrafiltration failure. Studies that compare 1.36%/1.5% dextrose or 2.27%/2.5% dextrose PET with 3.86%/4.25% dextrose PET are minimal. Because the 3.86%/4.25% test is recommended for the workup of ultrafiltration failure, more comparison data are needed. Furthermore, most kinetic modeling programs use data from 2.27%/2.5% dextrose PET to predict solute clearance and ultrafiltration. One needs to evaluate whether current kinetic modeling programs are as accurate if 4.25% PET is used; alternatively, if not, one may want to develop programs that use 4.25% dextrose PET data specifically. Once done, the standard PET may be changed to a 4.25% dextrose PET.

Guideline 6. Pediatric PD

Pediatric data are sparse, in part because there are few clinical trials using RR for death as an outcome for adequacy. However, there are other important aspects of overall patient care that need to be considered and evaluated. These include the development of a simplified means to estimate glomerular rate in children that precludes the need for urine collection and that is accurate at low levels (stages 4 to 5 CKD) of kidney function, determination of adequate and optimal total solute clearance in children receiving PD, comparison of the impact of peritoneal solute clearance versus RKF on patient outcome, evaluation of PD and the longevity of dialysis therapy on QOL of pediatric patients and their families, determination of the ability of icodextrin-based dialysis solutions to enhance ultrafiltration across the age/size spectrum of pediatrics, and evaluation of the safety and efficacy of ACE-inhibitor, ARB, and diuretic therapy in children with CKD stage 5 receiving PD.

IMPORTANT RESEARCH RECOMMENDATIONS

Guideline 1. Initiation of Dialysis

Much more research is needed regarding the impact on the patient of the period leading up to dialysis therapy and the period just after starting dialysis therapy. Additional research is needed on mood disorders, particularly depression and anger, that may develop during this period and the impact such disorders may have on outcomes after dialysis therapy is initiated.

Guideline 2. PD Solute Clearance Targets and Measurements

The presence of RKF was rather arbitrarily defined in this document by the Work Group as 100 mL of urine output per day. This was chosen because many of the studies on clearances chose 100 mL/d as the cutoff value. However, it is not clear that this is the most appropriate level of urine output to use, or even if urine volume, rather than measured GFR, would be preferable. Additional research is needed in this area.

Guideline 3. Preservation of RKF

Data for the effect of peritonitis on RKF are contradictory. Studies examining the impact of peritonitis, as well as the treatment approach, on RKF are needed. In particular, the severity of peritonitis may relate to loss of RKF with more severe episodes (for example, fungal or those caused by gram-negative bacilli) perhaps more likely leading to loss of RKF.

Guideline 4. Maintenance of Euvolemia

Euvolemia in home dialysis patients is not always readily achieved because patients may not be knowledgeable about this aspect of PD. A study examining training methods emphasizing evaluation of "euvolemia" as done by the patient on impact of blood pressure and volume status would be worthwhile. In addition, there are few, if any, studies of interventions to enhance patients' abilities to follow a rather rigorous diet in regard to sodium intake. Such studies should be undertaken.

Guideline 5. Quality Improvement Programs

Quality improvement programs are rather time consuming and therefore costly. A cost analysis of the impact of aggressive interventions by a program on outcomes should be carried out.

CPR for Guideline 3

Current guidelines recommend assessing peritoneal transport status by using PET. They subsequently recommend a hypertonic dwell (4.25% dextrose) to work up a patient with ultrafiltration failure. Studies that compare 1.36%/1.5% dextrose or 2.27%/2.5% dextrose PET with 3.86%/4.25% dextrose PET are minimal. Because the 3.86%/4.25% test is recommended for the workup of ultrafiltration failure, more comparison data are needed. Furthermore, most kinetic modeling programs use data from 2.27%/2.5% dextrose PET to predict solute clearance and ultrafiltration. One needs to evaluate whether current kinetic modeling programs are as accurate if 4.25% PET is used; alternatively, if not, one may want to develop programs that use 4.25% dextrose PET data specifically. Once done, the standard PET may be changed to a 4.25% dextrose PET.

RESEARCH RECOMMENDATIONS OF INTEREST

Guideline 1. Initiation of Dialysis

It is unclear whether it is advisable to start patients who chose cycler dialysis on therapy with a dry day. Theoretically, this might enhance long-term preservation of the peritoneal membrane, but there are no data concerning this. In addition, it is unclear whether a patient who wishes to dialyze at home using the cycler should be started initially on CAPD. The Work Group sees no reason for such an approach, but a study might be carried out to investigate the impact of each approach on QOL. Research on the desirability of placing a "backup" fistula in patients who chose PD therapy would be of interest.

Guideline 2. PD Solute Clearance Targets and Measurements

HD patients have a measure of small-solute adequacy carried out each month. There is considerable controversy among PD experts about the desirable frequency of measurements of peritoneal clearance, which tends not to change much over time. Studies evaluating this more carefully are warranted.

Guideline 3. Preservation of RKF

Because PD prescriptions often are dependent on RKF, it is important that the health care team recognize when RKF decreases. A study in which the PD patient measures the volume of urine output daily (such as transplant recipients historically were asked to do in the period immediately after transplantation) as a marker of RKF and to notify the dialysis program if there is a substantial change would be of some interest to see if this approach impacts on earlier recognition of an important change in RKF.

Guideline 4. Maintenance of Euvolemia

Patients on PD therapy traditionally are asked to monitor their own blood pressure at home, at a minimum daily. A study in which the patient measures blood pressure more often and takes an as-needed extra blood pressure medication for an elevation would be of interest to determine if this impacted on RKF or other outcomes.

Guideline 5. Quality Improvement Programs

Quality improvement programs traditionally are multidisciplinary. However, it is unclear how involved the physician or physician assistant typically is in many programs in the CQI efforts. An evaluation of the importance of having a "physician PD champion" in the multidisciplinary CQI process would be of interest.

Work Group Biographies

Joanne Bargman, MD, FRCPC, received her MD cum laude at the University of Toronto in 1978. After medical residency in Toronto, she was chosen as an exchange resident in Melbourne, Australia, where she completed her postgraduate year 3. She undertook nephrology training at Stanford University and, as a fellow of the Medical Research Council of Canada, spent almost 3 years in physiology research examining mechanisms of urinary concentration. She assumed a staff nephrologist position at the Toronto Western Hospital in 1985 and worked in the PD unit with Dimitrios Oreopoulos. She has published more than 120 articles and delivered more than 200 lectures internationally on subjects ranging from PD to glomerulonephritis and systemic lupus erythematosus. She is Director of the PD Program and also Co-Director of the Renal-Rheumatology Lupus Clinic at the University Health Network in Toronto. Dr Bargman is a council member of the International Society of Nephrology and the International Society of PD. She is the recipient of major teaching awards at the undergraduate and postgraduate levels at the University of Toronto. Dr Bargman has received research funds, grants, or contracts from Amgen, Baxter Healthcare, Fresenius Medical Care, and Gambro Healthcare.

Peter G. Blake, MD, FRCPC, MBBCh, is a Professor of Medicine and Chair of the Division of Nephrology at the University of Western Ontario and London Health Sciences Centre. He is a member of the Canadian Society of Nephrology Work Group on PD, was the editor of 2 major textbooks in nephrology, and is Editor-in-Chief of Peritoneal Dialysis International. His areas of interest include dialysis with particular regard to the development of PD, adequacy and nutrition in PD, trends in patient outcomes, and the economics of dialysis. Dr Blake has received lecture fees from Amgen, Baxter Healthcare, and Ortho Biotech.

John M. Burkart, MD (Co-Chair), is Professor of Medicine/Nephrology at Wake Forest Baptist Medical Center in Winston-Salem, NC. He is Corporate Medical Director of the Wake Forest University Outpatient Dialysis Centers. He attended medical school at Rush Medical College in Chicago, IL, and did his residency training and fellowship at the Bowman Gray School of Medicine of Wake Forest University. He has served on the PD Adequacy Work Group since its formation, currently as the Co-Chair. He is treasurer of the International Society for PD. He is a member of the Centers for Medicare and Medicaid Services advisory council for reimbursement based on case-mix. He has authored many chapters on PD in major nephrology text books and parts of Up to Date and is interested in all clinical aspects of PD and hemodialysis. Dr Burkart has received research funds, grants, or contracts from Baxter Healthcare, Genzyme, and Fresenius Medical Care.

Fredric O. Finkelstein, MD, is Chief of Nephrology, Hospital of St Raphael, and Clinical Professor of Medicine at Yale University, New Haven, CT. Dr Finkelstein has been involved in continuous ambulatory PD since 1979, when he started a freestanding continuous ambulatory PD facility in New Haven, CT. He has written extensively on a variety of issues involving PD therapy. He currently is a member of the Council of the

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Thomas A. Golper, MD, FACP, trained at Indiana University and the Oregon Health Sciences University and currently is Professor of Medicine (Nephrology) at Vanderbilt University Medical Center in Nashville, TN. He has held positions on the Board of Directors of the Renal Physicians Association and American Association of Kidney Patients, served as the PD Adequacy Work Group Chair for the first 2 versions of KDOQI, and remains on the Work Group and Steering Committee. He led the Network 9 Peritonitis and Catheter Survival Study and has served on the International Society of PD Ad Hoc Committee for Peritonitis for many iterations of its guidelines. His interests remain in the field of dialysis and the administrative aspects of nephrology practice. Dr Golper has received research funds, grants, or contracts from Amgen, Baxter Healthcare, Genzyme, Ortho Biotech, and Roche.

Angellina Graham, RN, graduated in 1995 with an associate degree in nursing. She is currently employed by Wake Forest Outpatient Dialysis at Piedmont Dialysis Center, serving in the role of Charge Nurse in the Hometraining Department and has also assisted with numerous clinical trials.

Beth Piraino, MD (Co-Chair), received her BS from the University of Pittsburgh. She attended medical school at the Medical College of Pennsylvania and graduated magna cum laude. She did her subsequent training in Internal Medicine and Nephrology at the University of Pittsburgh Health Center, after which she joined the faculty of the University of Pittsburgh School of Medicine, rising through the ranks over the years to her current position as tenured Professor of Medicine and Associate Dean of Admissions. Dr Piraino's major research interest has been to improve outcomes of patients on PD therapy, in particular, by decreasing infectious complications. She has published widely in the area of PD, with numerous presentations at national and international meetings. She was Secretary for the International Society of PD from 2001 to 2006. She is Director of the PD Program at the University of Pittsburgh and Co-Medical Director of Dialysis Clinic Inc of Oakland. She received the prestigious Life Time Achievement Award at the 24th Annual Dialysis Conference in February 2004 for contributions to the care of PD patients. Dr Piraino has received research funds, grants, or contracts from Paul Teschan Fund through Dialysis Clinic Inc. and Baxter Healthcare.

Susan Stark, MS, RD, CSR, LDN, is a dietitian specialist at the University of Pittsburgh Medical Center, Presbyterian Hospital. She is a member of the American Dietetic Association.

Bradley A. Warady, MD, is Chief of Nephrology and Director of Dialysis and Transplantation at The Children's Mercy Hospital and Professor of Pediatrics at the University of Missouri-Kansas City School of Medicine. Dr Warady's clinical and research focus is end-stage renal disease, with particular emphasis on PD. He established the Pediatric PD Study Consortium and is a member of the Board of Directors of the North American Pediatric Renal Transplant Cooperative Study. He currently serves as Co-Principal Investigator of the International Pediatric Peritonitis Registry and the National Institutes of

Health–funded Chronic Kidney Disease in Children (CKiD) study. He co-edited the books CAPD/CCPD in Children and Pediatric Dialysis and has published more than 200 articles and book chapters. He is a council member of the International Society of PD and has been a member of the KDOQI PD Adequacy, Pediatric Nutrition, and Pediatric Bone Work Groups for the National Kidney Foundation. Dr Warady also serves as an Associate Editor for Peritoneal Dialysis International and sits on the Editorial Board of Pediatric Nephrology. Dr Warady has received research funds, grants, or contracts from Amgen and Watson Pharmaceuticals.

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Michel Fischbach, MD, is Chief of the Pediatric Department at the University Hospital of Strasbourg and Professor of Pediatrics at the University Louis Pasteur of Strasbourg, France. Dr Fischbach's clinical and research focus is end stage renal disease with a special interest in hemodialysis and peritoneal dialysis. As a member of the European Pediatric Dialysis Work Group (EPDWG), he published as a first author on the European Peritoneal Dialysis Guidelines (2002) for children. He is also the primary author in more than 100 international articles on dialysis in children and he serves as an Associate Editor for Pediatric Nephrology, Dialysis section.

Denis F. Geary, MB, MRCP(UK), FRCP(C), is a Professor at Department of Pediatrics in University of Toronto and Chief at Division of Nephrology, The Hospital for Sick Children. He is the past-President of the Canadian Association of Pediatric Nephrologists and his current areas of interest include nocturnal hemodialysis for children, antenatally diagnosed renal disease, growth in children with renal failure, and anemia in children with chronic renal failure. Dr Geary has received research funds, grants, or contracts from Amgen and Hoffman La Roche.

Franz Schaefer, MD, is Professor of Pediatrics and Chief of the Pediatric Nephrology division at Heidelberg University Medical Center. He established the Mid European Pediatric Peritoneal Dialysis Study Group (MEPPS) and the European Study Group on Progressive Chronic Kidney Disease in Children (ESCAPE). He currently serves as Co-Principal Investigator of the International Pediatric Peritonitis Registry and he is also a member of the European Pediatric PD Working Group. He has co-edited the book "Pediatric Dialysis" and has published more than 220 articles and book chapters. In addition, he is a current council member of the European Society for Pediatric Nephrology and serves as pediatric liaison officer at the council of the International Society of Peritoneal Dialysis. Dr Schaefer also serves as an Assistant Editor for Pediatric Nephrology and sits in the Editorial Boards

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Cornelis H. Schröder, MD, PhD, is Director of the Pediatric Nephrology, Dialysis, and Transplantation Department at the Wilhelmina Children's Hospital and Professor of Pediatric Nephrology at the University of Utrecht, The Netherlands. His main research focuses are hereditary glomerular diseases and kidney replacement therapy, with particular emphasis on peritoneal dialysis. He is a member of the European Pediatric Dialysis Working Group, and has published several guidelines on behalf of this group. He is the author of more than 150 articles and book chapters in the field of pediatric nephrology.

Professor Alan R. Watson, FRCP, is Director of the Children & Young People's Kidney Unit, Nottingham City Hospital and Professor of Paediatric Nephrology at the University of Nottingham, UK. His research interests have been in clinical nephrology including nutrition, dialysis, psychosocial aspects and ethics. He is the group coordinator of the European Dialysis Working Group, which has produced 7 published guidelines to date. Prof. Watson has published over 200 articles and book chapters and he is a Council member of the European Society for Paediatric Nephrology since 2003. He is also currently on the Editorial Boards of the British Journal of Renal Medicine and Peritoneal Dialysis International.

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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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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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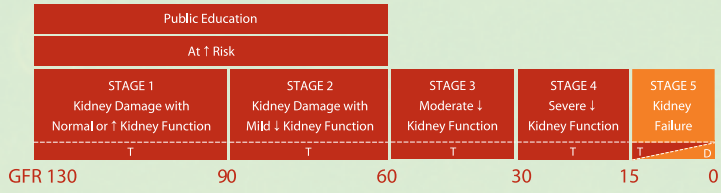

Light-shaded boxes indicate the scope of content targeted in this resource.
GFR = Glomerular Filtration Rate; T = Kidney Transplant; D = Dialysis

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